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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 20-F

(Mark One)

☐ **REGISTRATION STATEMENT PURSUANT TO SECTION 12(B) OR 12(G) OF THE SECURITIES EXCHANGE ACT OF 1934**

OR

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2022.

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934**

OR

☐ **SHELL COMPANY REPORT PURSUANT TO SECTION 13 OR 15(D) OF THE SECURITIES EXCHANGE ACT OF 1934**

Date of event requiring this shell company report _____

Commission file number: 001-39997

Adagene Inc.

(Exact name of Registrant as specified in its charter)

N/A

(Translation of Registrant's name into English)

Cayman Islands

(Jurisdiction of incorporation or organization)

4F, Building C14, No. 218
Xinghu Street, Suzhou Industrial Park
Suzhou, Jiangsu Province, 215123
People's Republic of China

(Address of principal executive offices)

Peter Luo
Chief Executive Officer
+86-512-87773616
Email:peter_luo@adagene.com
At the address of the Company set forth above

(Name, Telephone, E-mail and/or Facsimile number and Address of Company Contact Person)

Securities registered or to be registered pursuant to Section 12(b) of the Act:

Title of Each Class	Trading Symbol	Name of each exchange on which registered
American depositary shares, each ADS representing one and one quarter ordinary shares, par value US$0.0001 per share	ADAG	The Nasdaq Stock Market LLC (The Nasdaq Global Market)
Ordinary shares, par value US$0.0001 per share *	N/A	The Nasdaq Stock Market LLC (The Nasdaq Global Market)

* Not for trading, but only in connection with the listing on the Nasdaq Global Market of American depositary shares.

Securities registered or to be registered pursuant to Section 12(g) of the Act:

None
(Title of Class)

Securities for which there is a reporting obligation pursuant to Section 15(d) of the Act:

None
(Title of Class)

Indicate the number of outstanding shares of each of the issuer's classes of capital or common stock as of the close of the period covered by the annual report.

54,065,709 ordinary shares, par value US$0.0001 per share, as of December 31, 2022.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.

Yes ☐ No ☒

If this report is an annual or transition report, indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934.

Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files).

Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or an emerging growth company. See definition of "large accelerated filer," "accelerated filer," and "emerging growth company" in Rule 12b-2 of the Exchange Act. Check one:

Large Accelerated Filer ☐ Accelerated Filer ☒ Non-accelerated Filer ☐ Emerging growth company ☒

If an emerging growth company that prepares its financial statements in accordance with U.S. GAAP, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards † provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accountant firm that prepared or issued its audit report. Yes ☐ No ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to § 240.10D-1(b). ☐

Indicate by check mark which basis of accounting the registrant has used to prepare the financial statements included in this filing:

☒ U.S. GAAP

☐ International Financial Reporting Standards as issued by the International Accounting Standards Board

☐ Other

If "Other" has been checked in response to the previous question, indicate by check mark which financial statement item the registrant has elected to follow.

☐ Item 17 ☐ Item 18

If this is an annual report, indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

Yes ☐ No ☒

APPLICABLE ONLY TO ISSUERS INVOLVED IN BANKRUPTCY PROCEEDINGS DURING THE PAST FIVE YEARS

Indicate by check mark whether the registrant has filed all documents and reports required to be filed by Sections 12, 13 or 15(d) of the Securities Exchange Act of 1934 subsequent to the distribution of securities under a plan confirmed by a court.

Yes ☐ No ☐

† The term "new or revised financial accounting standard" refers to any update issued by the Financial Accounting Standards Board to its Accounting Standards Codification after April 5, 2012.

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INTRODUCTION

Except where the context otherwise indicates and for the purpose of this annual report only:

- "Adagene Suzhou" refers to Adagene (Suzhou) Limited, our subsidiary in the PRC;
- "Adagene Incorporated" reference to Adagene Incorporated, our subsidiary in the U.S.;
- "ADSs" refers to the American depositary shares, each representing one and one quarter (1.25) of our ordinary shares;
- "Antibody binding interface" or "antibody binding sites" refers to the antibody binding surface spots in contact with its recognition antigen;
- "China" or "PRC" refers to the People's Republic of China; and only in the context of describing PRC rules, laws, regulations, regulatory authority, and any PRC entities or citizens under such rules, laws and regulations and other legal or tax matters in this annual report, excludes Taiwan, Hong Kong, and Macau;
- "conformational diversity" or "dynamic diversity" refers to the existence of more than one conformation or structure due to dynamic fluctuation of the structures for a given protein sequence, independent of any conformational changes caused by external binding;
- "epitopes" or "epitope of an antigen" refers to the specific binding spots of an antigen in contact with its antibody binding surface;
- "Greater China," for the purpose of this annual report, refers to the People's Republic of China, Hong Kong, Macau and Taiwan;
- "multi-specificity" refers to a protein exerting a similar function (such as binding) on distinctly different ligands, perhaps while using different active site residues;
- "NEObody" refers to antibody designed with dynamic binding sites that adapt kinetically to unique epitopes through novel MOA, using our NEObody technology;
- "POWERbody" refers to antibody that utilizes our SAFEbody technology to create new bispecific T-cell engagers, antibody-drug conjugates, or antibodies, which are designed to reach beyond the therapeutic potency of traditional monospecific antibodies;
- "RMB" or "Renminbi" refers to the legal currency of the People's Republic of China;
- "SAFEbody" refers to antibody engineered with its binding sites masked, which are designed to be selectively activated in the TME, potentially limiting on-target off-tumor toxicity in normal tissues; SAFEbody® is a registered trademark in the United States, China, Australia, Japan, Singapore, and the European Union;

- “Securities Act” refers to the Securities Act of 1933, as amended;
- “species cross-reactivity” refers to reactivity of the same protein that recognizes and binds to similar epitopes of a given class of targets in different species;
- “US$,” “dollars” or “U.S. dollars” refers to the legal currency of the United States; and
- “we,” “us,” “our company,” and “our,” refer to Adagene Inc., a Cayman Islands exempted company and its subsidiaries.
- “NEObodies” refer to antibodies designed with dynamic binding sites that adapt kinetically to unique epitopes through novel MOAs, using our NEObody technology;
- “ordinary shares” or “shares” refers to our ordinary shares of par value US$0.0001 per share;
- “POWERbodies” refer to antibodies that utilize our SAFEbody technology to create new bispecific T-cell engagers, antibody-drug conjugates, or antibodies, which are designed to reach beyond the therapeutic potency of traditional monospecific antibodies; and
- “SAFEbodies” refer to antibodies engineered with their binding sites masked, which are designed to be selectively activated in the tumor microenvironment, potentially limiting on-target off-tumor toxicity in normal tissues.

FORWARD-LOOKING INFORMATION

This annual report contains forward-looking statements that reflect our current expectations and views of future events. All statements other than statements of historical facts are forward-looking statements. These forward-looking statements are made under the "safe harbor" provision under Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and as defined in the Private Securities Litigation Reform Act of 1995. These statements involve known and unknown risks, uncertainties and other factors, including but not limited to Adagene's ability to demonstrate the safety and efficacy of its drug candidates; the clinical results for its drug candidates, which may not support further development or regulatory approval; the content and timing of decisions made by the relevant regulatory authorities regarding regulatory approval of Adagene's drug candidates; Adagene's ability to achieve commercial success for its drug candidates, if approved; Adagene's ability to obtain and maintain protection of intellectual property for its technology and drugs; Adagene's reliance on third parties to conduct drug development, manufacturing and other services; Adagene's limited operating history and Adagene's ability to obtain additional funding for operations and to complete the development and commercialization of its drug candidates; Adagene's ability to enter into additional collaboration agreements beyond its existing strategic partnerships or collaborations, and the impact of the COVID-19 pandemic on Adagene's clinical development, commercial and other operations, as well as those risks more fully discussed in the "Risk Factors" section in Adagene's filings with the SEC. Such known and unknown risks, uncertainties and other factors may cause our actual results, performance or achievements to be materially different from those expressed or implied by the forward-looking statements. In some cases, you can identify these forward-looking statements by terminology such as "may," "will," "expect," "anticipate," "aim," "estimate," "intend," "plan," "believe," "is/are likely to," "potential," "continue" or other similar expressions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements include, but are not limited to, statements about:

- our goals and growth strategies;
- our future business development, results of operations and financial condition;
- the timing of the initiation, progress and potential results of our preclinical studies, clinical trials and our discovery programs;
- our ability to utilize our proprietary Dynamic Precision Library platform, or DPL, to design, construct and develop next-generation antibodies;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- the timing or likelihood of regulatory filings and approvals;
- our estimates of the number of patients who suffer from the diseases we are targeting and the number of patients that may enroll in our clinical trials;
- the commercializing of our product candidates, if approved;
- our ability and the potential to successfully manufacture and supply our product candidates for clinical trials and for commercial use, if approved;
- future strategic arrangements and/or collaborations and the potential benefits of such arrangements;
- our anticipated use of our existing resources and the proceeds from our initial public offering;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing and our ability to obtain additional capital;
- the sufficiency of our existing cash and cash equivalents to fund our future operating expenses and capital expenditure requirements;

- our ability to retain the continued service of our key personnel and to identify, hire and retain additional qualified professionals;
- the implementation of our business model, strategic plans for our business and product candidates;
- the scope of protection we are able to establish and maintain for intellectual property rights, such as our proprietary DPL, which includes NEObody platform, SAFEbody platform and POWERbody platform, product candidates and discovery programs;
- our potential to enter into new collaborations;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- the pricing, coverage and reimbursement of our product candidates, if approved;
- developments relating to our competitors and our industry, including competing product candidates and therapies;
- the direct and indirect impact of the COVID-19 pandemic on our business and operations and on development of our clinical and preclinical programs, and the duration and impact of COVID-19 or any of its variants that may affect, precipitate or exacerbate one or more of any of the risks and uncertainties mentioned in this annual report;
- relevant government policies and regulations relating to our business and industry;
- general economic and business condition in the markets we have businesses; and
- assumptions underlying or related to any of the foregoing.

We would like to caution you not to place undue reliance on these forward-looking statements and you should read these statements in conjunction with the risk factors disclosed in "Item 3. Key Information—D. Risk Factors" of this annual report and other risks outlined in our other filings with the Securities and Exchange Commission, or the SEC. Those risks are not exhaustive. We operate in an evolving environment. New risks emerge from time to time and it is impossible for our management to predict all risk factors and uncertainties, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statement. We qualify all of our forward-looking statements by these cautionary statements.

You should not rely upon forward-looking statements as predictions of future events. We do not undertake any obligation to update or revise the forward-looking statements except as required under applicable law. You should read this annual report and the documents that we reference in this annual report completely and with the understanding that our actual future results may be materially different from what we expect.

PART I

ITEM 1. IDENTITY OF DIRECTORS, SENIOR MANAGEMENT AND ADVISORS

Not applicable.

ITEM 2. OFFER STATISTICS AND EXPECTED TIMETABLE

Not applicable.

ITEM 3. KEY INFORMATION

3.A. [Reserved]

3.B. Capitalization and Indebtedness

Not applicable.

3.C. Reason for the Offer and Use of Proceeds

Not applicable.

3.D. Risk Factors

Summary of Risk Factors

Investors in Adagene Inc.'s equity securities are investing equity securities of a Cayman Islands holding company rather than equity securities of our subsidiaries that have substantive business operations in China or in the United States. Adagene Inc. is a Cayman Islands holding company that conducts a substantial portion of its operations in China through its PRC subsidiary, Adagene (Suzhou) Limited. In addition, Adagene Inc. conducts a substantial portion of its operations in the U.S. through its U.S. subsidiary, Adagene Incorporated. Our corporate group does not include any variable interest entities. Such structure involves unique risks to investors in the ADSs and ordinary shares. You should carefully consider all of the information in this annual report before making an investment in our ADSs. In particular, as we are a holding company with substantial business operations in China, you should pay special attention to subsections headed "Item 4.A.–– 4.A. History and Development of the Company Recent––Regulatory Developments," "Item 3.D. Risk Factors––Risks Related to Doing Business in the PRC," including but not limited to risk factor such as "uncertainties with respect to the PRC legal system, including uncertainties regarding the enforcement of laws, and sudden or unexpected changes in policies, laws and regulations in China could adversely affect us." The PRC government has significant authority to exert influence on the ability of a company with substantive operations in China, such as us, to conduct its business, accept foreign investments or list on a U.S. or other foreign exchanges. For example, we face risks associated with regulatory approvals of offshore offerings, anti-monopoly regulatory actions, oversight on cybersecurity and data privacy, as well as the lack of PCAOB inspection on our auditor. Such risks could result in a material change in our operations and/or the value of our ADSs or could significantly limit or completely hinder our ability to offer or continue to offer ADSs and/or other securities to investors and cause the value of such securities to significantly decline or be worthless. The PRC government also has significant oversight and discretion over the conduct of our business and as such may influence our operations at any time, which could result in a material adverse effect on our operations. The PRC government has recently published new policies and made statements, such as those related to regulatory approvals of offshore offerings and data security or anti-monopoly concerns, that although did not target on our company specifically, nevertheless have significantly affected certain industries and other PRC-based issuers as a whole, and we cannot rule out the possibility that it will in the future release regulations or policies regarding the industry where we operate, which could adversely affect our business, financial condition and results of operations. Furthermore, the PRC government has recently indicated an intent to exert more oversight and control over overseas securities offerings and other capital markets activities and foreign investment in China-based companies like us. These risks could result in a material change in our operations and the value of our ordinary shares or the ADSs, or could significantly limit or completely hinder our ability to conduct our business, accept foreign investments, or maintain listing on Nasdaq or list on other foreign exchange, and offer or continue to offer securities to investors, and cause the value of such securities to significantly decline or become worthless.

You should carefully consider all of the information in this annual report before making an investment in the ordinary shares or ADSs. Below please find a summary of the principal risks and uncertainties we face, organized under relevant headings. In particular, as we are a company incorporated in the Cayman Islands with substantive business operations in China, you should pay special attention to subsections headed "Item 3. Key Information—3.D. Risk Factors—Risks Related to Doing Business in the PRC" and "Item 3. Key Information—3.D. Risk Factors—Risks Related to the ADSs."

Below please find a summary of the principal risks we face, organized under relevant headings.

Risks Related to Doing Business in the PRC

Risks and uncertainties related to doing business in China include, but are not limited to, the following:

- Uncertainties with respect to the PRC legal system, including uncertainties regarding the enforcement of laws, and sudden or unexpected changes in policies, laws and regulations in China could adversely affect us. For details, see page 9 of this annual report;
- PRC government has significant oversight over the conduct of our business and as such may influence our operations at any time, which may potentially result in a material adverse effect on our operations. For details, see page 9 of this annual report;
- The PCAOB had historically been unable to inspect our auditor in relation to their audit work performed for our financial statements and the inability of the PCAOB to conduct inspections of our auditor in the past has deprived our investors with the benefits of such inspections. For details, see page 10 of this annual report.
- Our ADSs may be prohibited from trading in the United States under the HFCAA in the future if the PCAOB is unable to inspect or investigate completely auditors located in China. The delisting of the ADSs, or the threat of their being delisted, may materially and adversely affect the value of your investment. For details, see page 10 of this annual report;
- The enactment of the Accelerating Holding Foreign Companies Accountable Act decreases the number of non-inspection years from three years to two, thus reducing the time period before our ADSs will be prohibited from trading on the Nasdaq Stock Market or OTC or delisted. For details, see page 11 of this annual report;
- Your investments in our ADSs and/or ordinary shares are investments in equity securities of a Cayman Islands holding company rather than equity securities of our subsidiaries that have substantive business operations in China. As a result, you may experience difficulties in effecting service of legal process, enforcing foreign judgments or bringing actions in China against us or our management based on foreign laws. For details, see page 14 of this annual report;
- We may be required to obtain approval or complete filing or other requirements of the CSRC or other PRC government authorities in connection with our issuances of securities overseas, and, if required, we cannot predict whether we will be able to obtain such approval or complete such governmental procedure. For details, see page 16 of this annual report; and
- Substantial uncertainties exist with respect to the interpretation and implementation of the newly enacted Foreign Investment Law and how it may impact the viability of our current corporate structure, corporate governance and business operations. For details, see page 19 of this annual report.

Risks Related to Our Financial Prospects and Need for Additional Capital

Risks and uncertainties related to our financial prospectus and need for additional capital include, but are not limited to, the following:

- We have a limited operating history, which may make it difficult to evaluate our current business and predict our future performance. For details, see page 26 of this annual report;

- We have incurred net losses historically and we may continue to incur net losses in the near future. For details, see page 26 of this annual report;
- We may need to obtain substantial additional financing to fund our growth and operations, which may not be available on acceptable terms, if at all. For details, see page 27 of this annual report;
- Raising additional capital may lead to dilution of shareholdings by our existing shareholders and restrict our operations or require us to relinquish rights to our technologies or product candidates. For details, see page 28 of this annual report; and
- We have certain shareholders who have board representation rights and their individual interests may differ from yours. For details, see page 29 of this annual report.

Risks Related to Clinical Development of Our Product Candidates

Risks and uncertainties related to clinical development of our product candidates include, but are not limited to, the following:

- We may not be able to identify or discover new product candidates, and may allocate our limited resources to pursue a particular product candidate and fail to capitalize on product candidates that may later prove to be more profitable, or for which there is a greater likelihood of success. For details, see page 29 of this annual report;
- We may not be successful in our efforts to use and expand our proprietary platforms to build a pipeline of product candidates. For details, see page 30 of this annual report;
- Any failures or setbacks in our platforms or our other proprietary technologies could negatively affect our business and financial condition. For details, see page 30 of this annual report;
- Our product candidates, for which we intend to seek approval as biologic products, may face competition sooner than anticipated. For details, see page 30 of this annual report; and
- We depend substantially on the success of our product candidates, particularly our anti-CTLA-4 franchise, including ADG116 and ADG126, and our two anti-CD137 antibodies, ADG106 and ADG206, which are in clinical development, and our ability to identify additional product candidates. Clinical trials of our product candidates may not be successful. If we are unable to successfully identify new product candidates, complete clinical development, obtain regulatory approval and commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed. For details, see page 31 of this annual report.

Risks Related to Obtaining Regulatory Approval of Our Drug Candidates

Risks and uncertainties related to obtaining regulatory approval of our drug candidates include, but are not limited to, the following:

- The regulatory approval processes of the FDA, NMPA and other comparable regulatory authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approvals for our product candidates, our business will be substantially harmed. For details, see page 36 of this annual report.
- Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved or commercialized in a timely manner or at all, which could negatively impact our business. For details, see page 38 of this annual report.
- Even if we obtain FDA approval of any of our product candidates, we may never obtain approval or commercialize such products outside of the United States, which would limit our ability to realize their full market potential. For details, see page 38 of this annual report.

- We are conducting clinical trials and may in the future conduct additional clinical trials for our product candidates outside the United States and/or China, and FDA, NMPA and similar foreign regulatory authorities may not accept data from such trials. For details, see page 39

- Our product candidates may cause undesirable adverse events, side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following any regulatory approval. For details, see page 39 of this annual report.

Risks Related to Our Intellectual Property

Risks and uncertainties related to our intellectual property include, but are not limited to, the following:

- It is difficult and costly to protect our proprietary rights and technology, and we may not be able to protect our intellectual property rights throughout the world. For details, see page 64 of this annual report;

- Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates. For details, see page 67 of this annual report;

- We may not be successful in obtaining or maintaining necessary rights for our development pipeline through acquisitions and licensing deals. For details, see page 68 of this annual report;

- We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful, and any unfavorable outcome from such litigation could limit our research and development activities and/or our ability to commercialize our product candidates. For details, see page 69 of this annual report; and

- Our commercial success depends significantly on our ability to operate without infringing upon, misappropriating or otherwise violating the intellectual property rights of third parties. For details, see page 69 of this annual report.

Risks Related to the ADSs

Risks and uncertainties related to the ADSs include, but are not limited to, the following:

- Our business and financial results, including our ability to raise capital or raise capital on favorable terms and the market price of our ADSs, may be adversely affected by the geopolitical factors arising in connection with Russia’s invasion of Ukraine, including particularly how countries like the United States and China choose to respond to this war. As a result, the value of our ADSs may significantly decline. For details, see page 74 of this annual report.

- You may be subject to limitations on transfer of your ADSs. For details, see page 74 of this annual report;

- The trading price of the ADSs is likely to be volatile, which could result in substantial losses to investors. For details, see page 74 of this annual report;

- we are an emerging growth company within the meaning of the Securities Act and may take advantage of certain reduced reporting requirements. For details, see page 75 of this annual report;

- If securities or industry analysts cease to publish research or reports about our business, or if they adversely change their recommendations regarding the ADSs, the market price for the ADSs and trading volume could decline. For details, see page 75 of this annual report;

- The sale or availability for sale, or perceived sale or availability for sale, of substantial amounts of the ADSs could adversely affect their market price. For details, see page 75 of this annual report;

- We were likely a passive foreign investment company, or PFIC, for 2022, and there is a significant risk that we will be a PFIC for 2023 and possibly subsequent taxable years, in which case U.S. investors will generally be subject to adverse U.S. federal income tax consequences; and

- If a U.S. person is treated as owning 10% or more of our stock by vote or value, such person may be subject to adverse U.S. federal income tax consequences. For details, see page 81 of this annual report.

Risks Related to Doing Business in the PRC

Uncertainties with respect to the PRC legal system, including uncertainties regarding the enforcement of laws, and sudden or unexpected changes in policies, laws and regulations in China could adversely affect us.

Our operations in China are governed by the PRC laws and regulations. The PRC legal system is a civil law system based on written statutes. Unlike the common law system, prior court decisions under the civil law system may be cited for reference but have limited precedential value. In addition, any new PRC laws or changes in PRC laws and regulations related to, among other things, foreign investment and manufacturing in China could have a material adverse effect on our business and our ability to operate our business in China.

From time to time, we may have to resort to administrative and court proceedings to enforce our legal rights. Any administrative and court proceedings in China may be protracted, resulting in substantial costs and diversion of resources and management attention. Since PRC administrative and court authorities have significant discretion in interpreting and implementing statutory provisions and contractual terms, it may be more difficult to evaluate the outcome of administrative and court proceedings and the level of legal protection we enjoy, than in more developed legal systems. These uncertainties may impede our ability to enforce contracts in China and could materially and adversely affect our business and results of operations.

Furthermore, the PRC legal system is based in part on government policies and internal rules, some of which are not published on a timely basis, or at all, and may have retroactive effect. As a result, we may not be aware of our violation of any of these policies and rules until sometime after the violation. Such unpredictability towards our contractual, property and procedural rights could adversely affect our business, and impede our ability to continue our operations and proceed with our future business plans.

PRC government has significant oversight over the conduct of our business and as such may influence our operations at any time, which may potentially result in a material adverse effect on our operations.

PRC government has significant oversight over the conduct of our business and may intervene or influence our operations at any time, which may potentially result in a material adverse effect on our operations. PRC government has also recently indicated an intent to exert more oversight over offerings that are conducted overseas and foreign investment in China-based issuers, which could impact our ability to raise additional capital in international capital markets. In addition, the PRC government has recently published new policies that significantly affected certain industries such as the education and internet industries, and we cannot rule out the possibility that it will in the future release regulations or policies regarding our industry that could adversely affect our business, financial condition and results of operations. Any such action could significantly limit or completely hinder our ability to offer or continue to offer securities to investors and cause the value of such securities to significantly decline or be worthless.

However, as there are still regulatory uncertainties in this regard, we cannot assure you that we will be able to comply with new laws and regulations in all respects, and we may be ordered to rectify, suspend or terminate any actions or services that are deemed illegal by the regulatory authorities and become subject to material penalties, which may materially harm our business, financial condition, results of operations and prospects.

The PCAOB had historically been unable to inspect our auditor in relation to their audit work performed for our financial statements and the inability of the PCAOB to conduct inspections of our auditor in the past has deprived our investors with the benefits of such inspections.

Our auditor, the independent registered public accounting firm that issues the audit report included elsewhere in this annual report, as an auditor of companies that are traded publicly in the United States and a firm registered with the PCAOB, is subject to laws in the United States pursuant to which the PCAOB conducts regular inspections to assess its compliance with the applicable professional standards. The auditor is located in mainland China, a jurisdiction where the PCAOB was historically unable to conduct inspections and investigations completely before 2022. As a result, we and investors in the ADSs were deprived of the benefits of such PCAOB inspections. The inability of the PCAOB to conduct inspections of auditors in mainland China in the past has made it more difficult to evaluate the effectiveness of our independent registered public accounting firm's audit procedures or quality control procedures as compared to auditors outside of mainland China that are subject to the PCAOB inspections. On December 15, 2022, the PCAOB issued a report that vacated its December 16, 2021 determination and removed mainland China and Hong Kong from the list of jurisdictions where it is unable to inspect or investigate completely registered public accounting firms. However, if the PCAOB determines in the future that it no longer has full access to inspect and investigate completely accounting firms in mainland China and Hong Kong, and we use an accounting firm headquartered in one of these jurisdictions to issue an audit report on our financial statements filed with the Securities and Exchange Commission, we and investors in our ADSs would be deprived of the benefits of such PCAOB inspections again, which could cause investors and potential investors in the ADSs to lose confidence in our audit procedures and reported financial information and the quality of our financial statements.

Our ADSs may be prohibited from trading in the United States under the HFCAA in the future if the PCAOB is unable to inspect or investigate completely auditors located in China. The delisting of the ADSs, or the threat of their being delisted, may materially and adversely affect the value of your investment.

Pursuant to the HFCAA, if the SEC determines that we have filed audit reports issued by a registered public accounting firm that has not been subject to inspections by the PCAOB for two consecutive years, the SEC will prohibit our shares or ADSs from being traded on a national securities exchange or in the over-the-counter trading market in the United States.

On December 16, 2021, the PCAOB issued a report to notify the SEC of its determination that the PCAOB was unable to inspect or investigate completely registered public accounting firms headquartered in mainland China and Hong Kong and our auditor was subject to that determination. In May 2022, the SEC conclusively listed us as a Commission-Identified Issuer under the HFCAA following the filing of our annual report on Form 20-F for the fiscal year ended December 31, 2021. On December 15, 2022, the PCAOB removed mainland China and Hong Kong from the list of jurisdictions where it is unable to inspect or investigate completely registered public accounting firms. For this reason, we do not expect to be identified as a Commission-Identified Issuer under the HFCAA after we file this annual report on Form 20-F for the fiscal year ended December 31, 2022.

Each year, the PCAOB will determine whether it can inspect and investigate completely audit firms in mainland China and Hong Kong, among other jurisdictions. If the PCAOB determines in the future that it no longer has full access to inspect and investigate completely accounting firms in mainland China and Hong Kong and we use an accounting firm headquartered in one of these jurisdictions to issue an audit report on our financial statements filed with the Securities and Exchange Commission, we would be identified as a Commission-Identified Issuer following the filing of the annual report on Form 20-F for the relevant fiscal year. In accordance with the HFCAA, our securities would be prohibited from being traded on a national securities exchange or in the over-the-counter trading market in the United States if we are identified as a Commission-Identified Issuer for two consecutive years in the future. If our shares and ADSs are prohibited from trading in the United States, there is no certainty that we will be able to list on a non-U.S. exchange or that a market for our shares will develop outside of the United States. A prohibition of being able to trade in the United States would substantially impair your ability to sell or purchase our ADSs when you wish to do so, and the risk and uncertainty associated with delisting would have a negative impact on the price of our ADSs. Also, such a prohibition would significantly affect our ability to raise capital on terms acceptable to us, or at all, which would have a material adverse impact on our business, financial condition, and prospects.

The enactment of the Accelerating Holding Foreign Companies Accountable Act decreases the number of non-inspection years from three years to two, thus reducing the time period before our ADSs will be prohibited from trading on the Nasdaq Stock Market or OTC or delisted.

On June 22, 2021, the U.S. Senate passed a bill, also known as the Accelerating Holding Foreign Companies Accountable Act, to amend Section 104(i) of the Sarbanes-Oxley Act of 2002 (15 U.S.C. 7214(i)) to prohibit securities of any registrant from being listed on any of the U.S. securities exchanges or traded over-the-counter if the auditor of the registrant's financial statements is not subject to PCAOB inspection for two consecutive years, instead of three consecutive years as initially required under the HFCA Act, after the law becomes effective. On February 4, 2022, the U.S. House of Representatives passed the America COMPETES Act of 2022, which includes the exact same amendments as the bill passed by the Senate. On December 29, 2022, the Accelerating Holding Foreign Companies Accountable Act was signed into law as part of the recently passed fiscal year 2023 omnibus spending legislation. It requires the SEC to prohibit an issuer's securities from trading on U.S. markets if the SEC identifies such issuer to be a Commission-Identified Issuer for two consecutive years. Accordingly, it will reduce the time period before our ADSs will be prohibited from trading on the Nasdaq or over-the-counter or be delisted.

We may be restricted from transferring our scientific data abroad.

On March 17, 2018, the General Office of the PRC State Council promulgated the Measures for the Management of Scientific Data, or the Scientific Data Measures, which provide a broad definition of scientific data and relevant rules for the management of scientific data. According to the Scientific Data Measures, enterprises in China must seek governmental approval before any scientific data involving a state secret may be transferred abroad or to foreign parties. Further, any researcher conducting research funded, at least in part, by the PRC government is required to submit relevant scientific data for management by the entity to which such researcher is affiliated before such data may be published in any foreign academic journal. Currently, as the term "state secret" is not clearly defined, there is no assurance that we can always obtain relevant approvals for sending scientific data (such as the results of our preclinical studies or clinical trials conducted within China) abroad, or to our foreign partners in China.

Moreover, the Cyberspace Administration of China, or the CAC, issued the Measures on Security Assessment of the Cross-border Transfer of Personal Information (Draft for Comment) in June 2019, pursuant to which, any cross-border transfer of information that may endanger national security, damage public interest, or fail to offer effective protection of personal information security, as assessed by relevant regulatory bodies, will be prohibited. In July 2022, CAC issued the Measures on Security Assessment of the Cross-border Data Transfer, which regulates the thresholds for triggering mandatory security assessments not only in the cross-border transfers of personal information, but also in the cross-border transfers of "important data" collected and generated in China under certain circumstance. The term "important data" means any data, the tampering, damage, leakage, or illegal acquisition or use of which, if it happens, may endanger national security, the operation of the economy, social stability, public health and security, etc. Given that the government body will have full discretion in the assessment, it is unclear if and the extent to which our clinical data will be considered as an endangerment to national or personal information security.

Cross-border data transfer from other jurisdictions may also be limited if we fail to comply with relevant requirements, such as obtaining authorization from patients regarding the use, transfer and retrieval of their personal information or data and adopting measures to ensure the safety of personal information or data in the transfer. Also, cross-border transfer of personal data by its nature is subject to general data privacy regulations in various jurisdictions, and thus any failure to comply with data privacy protection may lead to a restriction of transferring our data across different jurisdictions.

If we are unable to obtain the necessary approvals in a timely manner, or at all, our research and development of product candidates may be hindered, which may materially and adversely affect our business, results of operations, financial conditions and prospects. If relevant government authorities consider the transmission of our scientific data to be in violation of the requirements under the Scientific Data Measures, we may be subject to specific administrative penalties imposed by those government authorities.

Failure to comply with existing or future laws and regulations related to privacy or data security could lead to government enforcement actions, which could include civil or criminal fines or penalties, private litigation, other liabilities, and/or adverse publicity. Compliance or the failure to comply with such laws could increase the costs of our products and services, limit their use or adoption, and otherwise negatively affect our operating results and business.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of personal information and important data worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Regulatory authorities in virtually every jurisdiction in which we operate have implemented and are considering a number of legislative and regulatory proposals concerning data protection.

Regulatory authorities in China have implemented and are considering a number of legislative and regulatory proposals concerning data protection. For example, China's Cybersecurity Law, which became effective in June 2017, established China's first national-level data protection for "network operators," which may include all organizations in China that connect to or provide services over the internet or other information network. The Cybersecurity Law requires network operators to perform certain functions related to cybersecurity protection. In addition, the Cybersecurity Law imposes certain requirements on network operators of critical information infrastructure, or the CIIOs. For example, the CIIOs generally shall, during their operations in the PRC, store the personal information and important data collected and produced within the territory of PRC, and shall perform certain security obligations as required under the Cybersecurity Law, including that the CIIOs shall pass the national security review when purchasing network product or service which may affect national security. In addition, China's Data Security Law, which was promulgated by the Standing Committee of PRC National People's Congress, or the SCNPC, on June 10, 2021 and came into effect on September 1, 2021, outlines the main system framework of data security protection. For example, the Data Security Law introduces a data classification and hierarchical protection system based on the importance of data in economic and social development, as well as the degree of harm it will cause to national security, public interests, or legitimate rights and interests of individuals or organizations when such data is tampered with, destroyed, leaked, or illegally acquired or used. Processors of "important data" are further required to conduct periodic risk assessment and submit assessment report to relevant regulatory authorities. In addition, the Data Security Law provides a national security review procedure for those data activities which may affect national security. Furthermore, Regulations on the Security Protection of Critical Information Infrastructure, which was promulgated by the State Council of PRC on July 30, 2021 and came into effect on September 1, 2021, or the CII Protection Regulations, stipulates the obligations and liabilities of the regulators, society and CIIOs in protecting the security of critical information infrastructure, or the CII. According to the CII Protection Regulations, regulators supervising specific industries shall formulate detailed guidance to recognize the CII in the respective sectors, and CIIOs shall take the responsibility to protect the CII's security by performing certain prescribed obligations. For example, CIIOs are required to conduct network security test and risk assessment, report the assessment results to relevant regulatory authorities, and timely rectify the issues identified at least once a year.

The Opinions on Strictly Cracking Down Illegal Securities Activities in Accordance with the Law, which were issued by the General Committee and State Council on July 6, 2021, require the speed-up of the revision of the provisions on strengthening the confidentiality and archives coordination between regulators related to overseas issuance and listing of securities, and improvement to the laws and regulations related to data security, cross-border data flow, and management of confidential information. Numerous regulations, guidelines and other measures have been or are expected to be adopted under the umbrella of, or in addition to the Cybersecurity Law and Data Security Law , including the Cybersecurity Review Measures published by Cyberspace Administration of China, or the CAC, and other 12 relevant PRC government authorities in December 2021, which provides that, among others, if a "network platform operator" that possesses personal information of more than one million users intends to go public in a foreign country, it must apply for a cybersecurity review with the Cybersecurity Review Office, and that the relevant PRC governmental authorities may initiate cybersecurity review if they determine certain network products, services, or data processing activities affect or may affect national security.

In July 2022, CAC issued the Measures on Security Assessment of the Cross-border Data Transfer, or the Security Assessment Measures, which provide that data processors shall make self-assessment of the risks before transferring data cross-border, and shall apply for security assessment for cross-border data transfer in any of the following circumstances: (i) outbound transfer of important data by a data processor; (ii) outbound transfer of personal information by CIIO Operators or a personal information processor who has processed the personal information of more than 1,000,000 people; (iii) outbound transfer of personal information by a personal information processor who has made outbound transfers of the personal information of 100,000 people cumulatively or the sensitive personal information of 10,000 people cumulatively since 1 January of the previous year; or (iv) other circumstances where an application for the security assessment of an outbound data transfer is required as prescribed by the national cyberspace administration authority.

In addition, the CAC published the Regulations for the Administration of Cyber Data Security (Draft for Comment), or the Draft Data Security Regulations, for public comments in November 2021, which reiterate that a data processor who processes personal information of more than one million individuals must complete the cybersecurity review if it intends to be listed in a foreign country, and if a data processor conducts any data processing activities that affect or may affect national security, an application for cybersecurity review shall also be made by such a processor. The Draft Data Security Regulations also require that data processors who process important data or whose securities are listed outside of China shall carry out annual data security assessment by itself or through a third party data security service provider and submit the assessment report to local agency of the CAC. Also see “Item 4. Information on the Company—4.B. Business Overview—Regulation—Other PRC Government Regulations—Regulations on Information Security and Data Protection” for detailed discussion.

As of the date of this annual report, the exact scope of CIIOs and important data under the current laws, regulations and regulatory regime remains unclear, and the authorities may have wide discretion in the interpretation and enforcement of the related laws and regulations. If we are deemed as a CIIO, or as an operator who collects, uses and processes important data according to the Cybersecurity Law, Data Security Law and other relevant laws and regulations, we may need to perform or be subject to certain prescribed obligations, and if we were found to be in violation of these applicable laws and regulations, we may be subject to administrative penalties, including fines and service suspension. We also cannot rule out the possibility that certain of our customers may be deemed as CIIOs, or as operators processing important data, in which case our products or services or data processing activities, if being deemed as related to national security, will need to be submitted for cybersecurity review before we can enter into agreements with such customers, and before the conclusion of such procedure, the customers will not be allowed to use our products or services. If the reviewing authority considers that the use of our services by certain of our customers involves risk of disruption, is vulnerable to external attacks, or may negatively affect, compromise, or weaken the protection of national security, we may not be able to provide our products or services to such customers, which could have a material adverse effect on our results of operations and business prospects.

As of the date of this annual report, we have not been involved in any investigations on cybersecurity review initiated by the Cyberspace Administration of China, and we have not received any inquiry, notice, warning, sanctions in such respect or any regulatory objections to our listing status on the Nasdaq. As there are still uncertainties regarding the further enaction of new laws and regulations as well as the revision, interpretation and implementation of those existing laws and regulations, however, we cannot assure you that we will be able to comply with such regulations in all respects, and we may be ordered to rectify, suspend or terminate any actions or services that are deemed illegal or incompliance by the regulatory authorities and become subject to fines and/or other penalties. If we are unable to address such issue in a timely manner or at all, we may be required to suspend or terminate our related businesses or face other penalties, our business, financial condition, results of operations, and prospects could be materially harmed.

Furthermore, certain PRC regulatory authorities recently issued the Opinions on Strictly Cracking Down on Illegal Securities Activities. These opinions call for strengthened regulation over illegal securities activities and supervision of overseas listings by China-based companies and propose to take effective measures. As of the date of this annual report, no official guidance or related implementation rules have been issued and taken into effect in relation to such opinions and as a result, the interpretation and implementation of these opinions remain unclear at this stage. We cannot assure you that we will not be required to obtain the pre-approval of the CSRC and potentially other regulatory authorities to pursue an offering of securities overseas or to maintain the listing status of our ADSs on the Nasdaq. See also “––We may be required to obtain approval or complete filing or other requirements of the CSRC or other PRC government authorities in connection with our issuances of securities overseas, and, if required, we cannot predict whether we will be able to obtain such approval or complete such governmental procedure.”

In addition, certain industry-specific laws and regulations affect the collection and transfer of personal data in China. For example, the PRC State Council promulgated Regulations on the Administration of Human Genetic Resources (effective in July 2019), which require approval from or filings with the Science and Technology Administration Department of the State Council where human genetic resources, or HGR, are involved in any international collaborative project and additional approval for any export or cross-border transfer of the HGR samples or human genetic resource information. In addition, the Ministry of Science and Technology of the PRC published the Implementing Rules of the Administrative Regulations on Human Genetic Resources (Draft for Comment), which refined the requirements related to the ethical review required in the collection, conservation, utilization, and external provision of HGR.

It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices, potentially resulting in confiscation of HGR samples and human genetic resource information and administrative fines or in worst cases, criminal penalties. In addition, the interpretation and application of data and personal information protection laws in China and elsewhere are often uncertain and in flux.

Dividends we receive from our subsidiaries located in the PRC may be taxed at a higher rate, which could materially and adversely affect the amount of dividends, if any, we may pay our shareholders.

Pursuant to the Double Tax Avoidance Arrangement between Hong Kong and China, or the Double Tax Avoidance Treaty, and the Notice on Certain Issues with Respect to the Enforcement of Dividend Provisions in Tax Treaties, or the Notice on Tax Treaties, issued on February 20, 2009 by the State Administration of Taxation of the PRC, or the SAT, if a Hong Kong resident enterprise owns more than 25% of the equity interest of a PRC company at all times during the twelve-month period immediately prior to obtaining a dividend from such company, the 10% withholding tax on such dividend is reduced to 5%, provided that certain other conditions and requirements under the Double Tax Avoidance Treaty and other applicable PRC laws are satisfied at the discretion of the relevant PRC tax authority. However, based on the Notice on Tax Treaties, if the relevant PRC tax authorities determine, in their discretion, that a company benefits from such reduced income tax rate due to a structure or arrangement that is primarily tax-driven, the PRC tax authorities may adjust the preferential tax treatment. Based on the Notice on Issues concerning Beneficial Owner in Tax Treaties, or Circular 9, issued on February 3, 2018 by the SAT and effective on April 1, 2018, when determining the applicant's status as a "beneficial owner" for purpose of tax treatments in connection with dividends, interests or royalties in the tax treaties, several factors will be taken into account, and it will be analyzed according to the actual circumstances of the specific cases. If our Hong Kong subsidiary is determined by PRC government authorities as receiving benefits from reduced income tax rates due to a structure or arrangement that is primarily tax-driven, the dividends paid by our PRC subsidiaries to our Hong Kong subsidiary will be taxed at a higher rate, which will have an adverse effect on our financial and operational conditions.

Your investments in our ADSs and/or ordinary shares are investments in equity securities of a Cayman Islands holding company rather than equity securities of our subsidiaries that have substantive business operations in China for instance. As a result, you may experience difficulties in effecting service of legal process, enforcing foreign judgments or bringing actions in China against us or our management based on foreign laws.

Adagene Inc. is a holding company incorporated under the laws of the Cayman Islands with no operations of its own. It conducts a substantial portion of its operations in China primarily through its subsidiary in China, Adagene (Suzhou) Limited. In addition, Adagene Inc. conducts a substantial portion of its operations in the U.S. through its U.S. subsidiary, Adagene Incorporated. As such, investors in the ADSs or ordinary shares are not purchasing equity securities of our subsidiaries that have substantive business operations in China or in the U.S. but instead are purchasing equity securities of a Cayman Islands holding company. In addition, some of our senior executive officers and directors reside within China for a significant portion of the time and some are PRC nationals. As a result, it may be difficult for our shareholders or investors to effect service of process upon us or those persons inside China. In addition, China does not have treaties providing for the reciprocal recognition and enforcement of judgments of courts with the Cayman Islands and many other countries and regions. Therefore, recognition and enforcement in China of judgments of a court in any of these non-PRC jurisdictions in relation to any matter not subject to a binding arbitration provision may be difficult or impossible.

Shareholder claims that are common in the United States, including securities law class actions and fraud claims, generally are difficult to pursue as a matter of law or practicality in China. For example, in China, there are significant legal and other obstacles to obtaining information needed for shareholder investigations or litigation outside China or otherwise with respect to foreign entities. Although the local authorities in China may establish a regulatory cooperation mechanism with the securities regulatory authorities of another country or region to implement cross-border supervision and administration, such regulatory cooperation with the securities regulatory authorities in the Unities States have not been efficient in the absence of mutual and practical cooperation mechanism. According to Article 177 of the PRC Securities Law which became effective in March 2020, no overseas securities regulator is allowed to directly conduct investigation or evidence collection activities within the territory of the PRC. Accordingly, without the consent of the competent PRC securities regulators and relevant authorities, no organization or individual may provide the documents and materials relating to securities business activities to overseas parties. See also "Item 3 Key Information—Risk Factors—Risks Related to the ADSs—You may face difficulties in protecting your interests, and your ability to protect your rights through U.S. courts may be limited, because we are incorporated under Cayman Islands law."

Recent litigation and negative publicity surrounding China-based companies listed in the United States may result in increased regulatory scrutiny of us and negatively impact the trading price of the ADSs and could have a material adverse effect upon our business, including our results of operations, financial condition, cash flows and prospects.

We believe that litigation and negative publicity surrounding companies with operations in China that are listed in the United States have negatively impacted stock prices for these companies. Various equity-based research organizations have published reports on China-based companies after examining their corporate governance practices, related party transactions, sales practices and financial statements, and these reports have led to special investigations and listing suspensions on U.S. national exchanges. Any similar scrutiny of us, regardless of its lack of merit, could result in a diversion of management resources and energy, potential costs to defend ourselves against rumors, decreases and volatility in the ADS trading price, and increased directors and officers insurance premiums and could have an adverse effect upon our business, including our results of operations, financial condition, cash flows and prospects.

Changes in U.S. and international trade policies, particularly with regard to China, may adversely impact our business and operating results.

Although cross-border business may not be an area of our focus, if we plan to expand our business internationally in the future, any unfavorable government policies on international trade, such as capital controls or tariffs, may affect the demand for our products and services, impact our competitive position, or prevent us from being able to conduct business in certain countries. If any new tariffs, legislation, or regulations are implemented, or if existing trade agreements are renegotiated, such changes could adversely affect our business, financial condition, and results of operations. Recently, there have been heightened tensions in international economic relations, such as the one between the United States and China. The U.S. government has recently imposed, and has recently proposed to impose additional, new, or higher tariffs on certain products imported from China to penalize China for what it characterizes as unfair trade practices. China has responded by imposing, and proposing to impose additional, new, or higher tariffs on certain products imported from the United States. Following mutual retaliatory actions for months, on January 15, 2020, the United States and China entered into the Economic and Trade Agreement Between the United States of America and the People's Republic of China as a phase one trade deal, effective on February 14, 2020. It remains unclear what additional actions, if any, will be taken by the U.S. or other governments with respect to international trade, tax policy related to international commerce, or other trade matters. The situation is further complicated by the political tensions between the United States and China that escalated during the COVID-19 pandemic and in the wake of the PRC National People's Congress' decision on Hong Kong national security legislation, sanctions imposed by the U.S. Department of Treasury on certain officials of the Hong Kong Special Administrative Region and the central government of the PRC and the executive orders issued by U.S. President in August 2020 that prohibit certain transactions with certain China-based companies and their respective subsidiaries. Rising trade and political tensions could reduce levels of trade, investments, technological exchanges and other economic activities between China and other countries, which would have an adverse effect on global economic conditions, the stability of global financial markets, and international trade policies.

Although the direct impact of the current international trade and political tension, and any escalation of such tension, on the biopharmaceutical companies in China is uncertain, the negative impact on general, economic, political and social conditions may adversely impact our business, financial condition and results of operations.

We may be required to obtain approval or complete filing or other requirements of the CSRC or other PRC government authorities in connection with our issuances of securities overseas, and, if required, we cannot predict whether we will be able to obtain such approval or complete such governmental procedure.

The M&A Rules requires an overseas special purpose vehicle formed for listing purposes through acquisitions of PRC domestic companies and controlled by PRC companies or individuals to obtain the approval of the CSRC prior to the listing and trading of such special purpose vehicle's securities on an overseas stock exchange. However, the application of the M&A Rules remains unclear. If CSRC approval is required for any of our future offerings of securities overseas or to maintain the listing status of the ADSs, it is uncertain whether it would be possible for us to obtain the approval, and any failure to obtain or delay in obtaining such approval would subject us to sanctions imposed by the CSRC and other PRC government authorities.

In addition, the General Office of the Central Committee of the Communist Party of China and the General Office of the State Council jointly issued the "Opinions on Severely Cracking Down on Illegal Securities Activities According to Law" ("Opinions") which were made available to the public on July 6, 2021. The Opinions emphasized the need to strengthen the administration over illegal securities activities and the supervision on overseas listings by China-based companies. These Opinions proposed to take effective measures, such as promoting the construction of relevant regulatory systems, to deal with the risks and incidents facing China-based overseas-listed companies and the demand for cybersecurity and data privacy protection. The policies described above and any related implementation rules to be enacted may subject us to additional compliance requirement in the future. As the Opinions only provide general guidance, the interpretation and implementation of the Opinions remain unclear in several respects at this time. Therefore, we cannot assure you that we will remain fully compliant with all new regulatory requirements of the Opinions or any future implementation rules on a timely basis, or at all.

On December 24, 2021, the CSRC issued the Provisions of the State Council on the Administration of Overseas Securities Offering and Listing by Domestic Companies (Draft for Comments) and the Administrative Measures for the Filing of Overseas Securities Offering and Listing by Domestic Companies (Draft for Comments), collectively the Draft Overseas Listing Regulations, for public comment until January 23, 2022. Following issuance of the Draft Overseas Listing Regulations, on February 17, 2023, the CSRC issued the Notice on Filing Arrangements for Overseas Securities Offering and Listing by Domestic Companies (the "CSRC Filing Notice"), stating that the CSRC has published the Trial Administrative Measures of Overseas Securities Offering and Listing by Domestic Companies (the "Trial Measures") and five supporting guidelines (the "Listing Guidelines"), collectively the Trial Measures and Listing Guidelines, which came into effect on March 31, 2023.

The Trial Measures provide that an overseas listing or offering securities (which, for the purposes of the Trial Measures, are defined thereunder as equity shares, depository receipts, corporate bonds convertible to equity shares, and other equity securities that are offered and listed overseas, either directly or indirectly, by PRC domestic companies) is explicitly prohibited under any of the following circumstances: (i) such securities offering and listing is explicitly prohibited by provisions in laws, administrative regulations and relevant state rules of the PRC; (ii) the intended securities offering and listing may endanger national security as reviewed and determined by competent authorities under the State Council in accordance with law; (iii) the domestic company, its controlling shareholder(s) or the actual controller have committed relevant crimes such as corruption, bribery, embezzlement, misappropriation of property or undermining the order of the socialist market economy during the latest three years; (iv) the domestic company is currently under investigations for suspicion of criminal offenses or major violations of laws and regulations, and no conclusion has yet been made thereof; or (v) there are material ownership disputes over equity held by the domestic company's controlling shareholder(s) or by other shareholder(s) that are controlled by the controlling shareholder(s) and/or actual controller.

A filing-based regulatory regime is adopted to regulate both direct and indirect overseas securities offering and listing by the domestic companies undert the Trial Measures. Direct overseas offering and listing by domestic companies refers to such overseas offering and listing by a joint-stock company incorporated domestically, while the indirect overseas offering and listing by domestic companies refers to the offering and listing by a company in the name of an overseas incorporated entity which major business operations are located domestically and such offering and listing is based on the underlying equity, assets, earnings or other similar rights of a domestic company.

The Trial Measures stipulate that an overseas listing will be determined as "indirect" if the issuer meets both of the following conditions: (1) 50% or more of any of the issuer's operating revenue, total profit, total assets or net assets as documented in its audited consolidated financial statements for the most recent accounting year are accounted for by PRC domestic companies ("Condition I"), and (2) the main parts of the issuer's business activities are conducted in the PRC, or its main places of business are located in the PRC, or the senior managers in charge of its business operations and management are mostly Chinese citizens or domiciled in the PRC ("Condition II"); whether Chinese citizens from Taiwan, Hong Kong, and Macau are included in the foregoing specification is not specified. The determination as to whether or not an overseas offering and listing by PRC domestic companies is indirect shall be made on a "substance over form" basis; the Listing Guidelines further stipulate that if an issuer not satisfying Condition I submits an application for issuance and listing in overseas markets in accordance with relevant non-PRC issuance regulations requiring such issuer to disclose risk factors mainly related to the PRC, the securities firm(s) and the issuer's PRC counsel should follow the principle of "substance over form" in order to identify and argue whether the issuer should complete a filing under the Trial Measures.

Subsequent securities offerings of an issuer in (i) the same overseas market where it has previously offered and listed securities, and (ii) an overseas market other than one where the issuer has previously offered and listed securities shall be filed with the CSRC within three working days after offerings are completed. Additionally, the Trial Measures stipulate that after an issuer has offered and listed securities in an overseas market, the issuer shall submit a report to the CSRC within three working days after the occurrence and public disclosure of (i) a change of control thereof, (ii) investigations of or sanctions imposed on the issuer by overseas securities regulators or relevant competent authorities, (iii) changes of listing status or transfers of listing segment, and (iv) a voluntary or mandatory delisting.

The CSRC Filing Notice states that, beginning from March 31, 2023, PRC domestic enterprises which have already issued and listed securities overseas and fall within the scope of filing under the Trial Measures shall be considered "existing enterprises" ("Existing Listed Enterprises"). Existing Listed Enterprises are not required to complete filings immediately; rather, Existing Listed Enterprises should complete filings if they are subsequently involved in matters require filings, such as follow-on financing activities, in accordance with the Trial Measures.

As advised by our PRC legal counsel, Jingtian & Gongcheng, in the event that the issuer does not meet either Condition I or Condition II, the filing requirements under the Trial Measures will not apply. However, we cannot assure you that our relevant indicators listed in Condition I and Condition II will not change in the future nor that the CSRC will agree with our determination. To the extent we are deemed as a PRC domestic company that is subject to the CSRC filing, we may be further deemed as an Existing Listed Enterprise as defined under the CSRC Filing Notice, and that future offerings of listed securities or listings outside China by us or voluntary delisting may be subject to CSRC filing requirements in accordance with the Trial Measures. Given that the Trial Measures and Listing Guidelines have been introduced recently, and that there remain substantial uncertainties surrounding the enforcement thereof, we cannot assure you that, if required, we would be able to complete the filings and fully comply with the relevant new rules on a timely basis, if at all.

In addition, the Measures for Cybersecurity Review, which took effect on February 15, 2022, requires, among others, prior cybersecurity review for online platform operators holding over one million users' personal information before any public listing in a foreign country. The Measures on Security Assessment of Cross-border Data Transfer, effective on September 1, 2022, specify that data controllers and/or critical information infrastructure operators will be subject to security assessment. There remain uncertainties as to whether such measures are applicable to our business. See also "——Failure to comply with existing or future laws and regulations related to privacy or data security could lead to government enforcement actions, which could include civil or criminal fines or penalties, private litigation, other liabilities, and/or adverse publicity. Compliance or the failure to comply with such laws could increase the costs of our products and services, limit their use or adoption, and otherwise negatively affect our operating results and business."

On February 24, 2023, the CSRC and other PRC governmental authorities jointly issued the Provisions on Strengthening Confidentiality and Archives Administration of Overseas Securities Offering and Listing by Domestic Companies (the "Confidentiality Provisions"), which will come into effect on March 31, 2023. According to the Confidentiality Provisions, PRC domestic companies that directly or indirectly conduct overseas offerings and listings shall strictly abide by the laws and regulations on confidentiality when providing or publicly disclosing, whether directly or through their overseas listed entities, materials to securities services providers. In the event such materials contain state secrets or working secrets of government agencies, PRC domestic companies shall first obtain approval from authorities, and file with the secrecy administrative department at the same level with the approving authority; in the event that such materials, if divulged, will jeopardize national security or public interest, PRC domestic companies shall comply with procedures stipulated by national regulations. PRC domestic companies shall also provide a written statement of the specific sensitive information provided when providing materials to securities service providers, and such written statements shall be retained for inspection. As the Confidentiality Provisions were recently promulgated and are yet to take effect, their interpretation and implementation remain substantially uncertain.

If (i) we mistakenly conclude that certain regulatory filings, permissions and approvals are not required or (ii) applicable laws, regulations, or interpretations change and (iii) we are required to obtain such filings, permissions or approvals in the future, we may be unable to obtain them in a timely manner, or at all, and such filings, permissions or approvals may be denied or rescinded even if obtained. We may face adverse actions or sanctions by the CSRC or other PRC regulatory agencies if we are unable to comply with such requirements, which may result in fines and penalties, restrictions on our operations, having to delist from a stock exchange outside of China, the halting of securities offerings to foreign investors and other actions that could materially and adversely affect our operations and the interest of our investors and cause a significant depreciation in the price of our ordinary shares and ADSs.

If we are classified as a PRC resident enterprise for PRC income tax purposes, such classification could result in unfavorable tax consequences to us and our non-PRC shareholders or ADS holders.

Under the PRC Enterprise Income Tax Law and its implementation rules, an enterprise established outside of the PRC with a "de facto management body" within the PRC is considered a "resident enterprise" and will be subject to the enterprise income tax on its global income at the rate of 25%. The implementation rules define the term "de facto management body" as the body that exercises full and substantial control over and overall management of the business, productions, personnel, accounts and properties of an enterprise. In 2009, SAT issued a circular, known as SAT Circular 82, which provides certain specific criteria for determining whether the "de facto management body" of a PRC-controlled enterprise that is incorporated offshore is located in China. Although this circular only applies to offshore enterprises controlled by PRC enterprises or PRC enterprise groups, not those controlled by PRC individuals or foreigners, the criteria set forth in the circular may reflect the SAT's general position on how the "de facto management body" test should be applied in determining the tax resident status of all offshore enterprises. According to SAT Circular 82, an offshore incorporated enterprise controlled by a PRC enterprise or a PRC enterprise group will be regarded as a PRC tax resident by virtue of having its "de facto management body" in China and will be subject to PRC enterprise income tax on its global income only if all of the following conditions are met: (i) the primary location of the day-to-day operational management and the places where they perform their duties are in the PRC; (ii) decisions relating to the enterprise's financial and human resource matters are made or are subject to approval by organizations or personnel in the PRC; (iii) the enterprise's primary assets, accounting books and records, company seals, and board and shareholder resolutions, are located or maintained in the PRC; and (iv) at least 50% of voting board members or senior executives habitually reside in the PRC.

We believe that we are not a PRC resident enterprise for PRC tax purposes. See "Item 10 Additional Information—Taxation— Material PRC Income Tax Considerations." However, the tax resident status of an enterprise is subject to determination by the PRC tax authorities and uncertainties remain with respect to the interpretation of the term "de facto management body." If the PRC tax authorities determine that we or any of our non-PRC subsidiaries are a PRC resident enterprise for enterprise income tax purposes, we or the subsidiary will be subject to PRC tax at a rate of 25%. In addition, we may be required to withhold taxes from dividends, and non-PRC shareholders (including ADS holders) may be subject to PRC tax on gains realized on the sale or other disposition of ADSs or ordinary shares, if such income is treated as sourced from within the PRC, as described below under "Item 3.D.Risk Factors—Risks Related to the ADS—You may be subject to PRC income tax on dividends from us or any gain realized on the transfer of our ADSs."

You may be subject to PRC income tax on dividends from us or on any gain realized on the transfer of our ADSs.

Under the Enterprise Income Tax Law of the PRC, or the EIT Law, and its implementation rules, PRC withholding tax at the rate of 10% is generally applicable to dividends from PRC sources paid to investors that are resident enterprises outside of China and that do not have an establishment or place of business in China, or that have an establishment or place of business in China but the relevant income is not effectively connected with the establishment or place of business. Any gain realized on the transfer of shares by such investors is subject to 10% PRC income tax if this gain is regarded as income derived from sources within China. Under the PRC Individual Income Tax Law and its implementation rules, dividends from sources within China paid to foreign individual investors who are not PRC residents are generally subject to a PRC withholding tax at a rate of 20% and gains from PRC sources realized by these investors on the transfer of shares are generally subject to 20% PRC income tax. Any such PRC tax liability may be reduced by the provisions of an applicable tax treaty.

Although we have substantial business operations in China, it is unclear whether the dividends we pay with respect to our shares or ADSs, or the gains realized from the transfer of our shares or ADSs, would be treated as income derived from sources within China and as a result be subject to PRC income tax if we were considered a PRC resident enterprise. If PRC income tax is imposed on gains realized through the transfer of our ADSs or on dividends paid to our non-resident investors, the value of your investment in our ADSs may be adversely affected. Furthermore, our shareholders whose jurisdictions of residence have tax treaties or arrangements with China may not qualify for, or able to obtain in practice, the benefits under these tax treaties or arrangements.

The biopharmaceutical industry in China is highly regulated and such regulations are subject to changes which may affect approval and commercialization of our product candidates.

Part of our research and development operations are in China, which we believe confers clinical, commercial and regulatory advantages. The biopharmaceutical industry in China is subject to comprehensive government regulation and supervision, encompassing the approval, registration, manufacturing, packaging, licensing and marketing of new product candidates. See “Item 4 Information on the Company—Regulation” for a discussion of the regulatory requirements that are applicable to our current and planned business activities in China. In recent years, the regulatory framework in China regarding the biopharmaceutical industry has undergone significant changes, and we expect that it will continue to undergo significant changes. Any such changes or amendments may result in increased compliance costs on our business or cause delays in or prevent the successful development or commercialization of our product candidates in China and reduce the current benefits we believe are available to us from developing and manufacturing drugs in China. PRC authorities have become increasingly vigilant in enforcing laws in the biopharmaceutical industry and any failure by us or our partners to maintain compliance with applicable laws and regulations or obtain and maintain required licenses and permits may result in the suspension or termination of our business activities fines, warnings, administrative or criminal penalties in China. We believe our strategy and approach are aligned with the PRC government’s regulatory policies, but we cannot ensure that our strategy and approach will continue to be aligned.

Substantial uncertainties exist with respect to the interpretation and implementation of the newly enacted Foreign Investment Law and how it may impact the viability of our current corporate structure, corporate governance and business operations.

On March 15, 2019, the PRC National People’s Congress approved the Foreign Investment Law, which came into effect on January 1, 2020 and replaces the trio of existing laws regulating foreign investment in the PRC, namely, the Sino-Foreign Equity Joint Venture Enterprise Law, the Sino-Foreign Cooperative Joint Venture Enterprise Law and the Wholly Foreign-Invested Enterprise Law, together with their implementation rules and ancillary regulations and become the legal foundation for foreign investment in the PRC. Meanwhile, the *Implementation Regulation of the Foreign Investment Law and the Measures for Reporting of Information on Foreign Investment* came into effect as of January 1, 2020, which clarified and elaborated the relevant provisions of the*Foreign Investment Law*.

The Foreign Investment Law sets out the basic regulatory framework for foreign investments and proposes to implement a system of pre-entry national treatment with a negative list for foreign investments, pursuant to which (i) foreign entities and individuals are prohibited from investing in the areas that are not open to foreign investments, (ii) foreign investments in the restricted industries must satisfy certain requirements under the law, and (iii) foreign investments in business sectors outside of the negative list will be treated equally with domestic investments. The Foreign Investment Law also sets forth necessary mechanisms to facilitate, protect and manage foreign investments and proposes to establish a foreign investment information reporting system, through which foreign investors or foreign-invested enterprises are required to submit initial report, report of changes, report of deregistration and annual report relating to their investments to the Ministry of Commerce, or MOFCOM, or its local branches.

Our business may be negatively affected by the potential obligations to make additional social insurance and housing fund contributions.

We are required by PRC labor laws and regulations, such as the Social Insurance Law, Administrative Regulations on the Housing Provident Fund and other related rules, to pay various statutory employee benefits, including pensions insurance, medical insurance, work-related injury insurance, unemployment insurance, maternity insurance and housing fund, to designated government agencies for the benefit of our employees. The relevant government agencies may examine whether an employer has made adequate and timely payments of the requisite statutory employee benefits, and employers who fail to make adequate and timely payments may be subject to supplemental contributions, late payment fees, fines compulsory enforcement and/or other penalties. If the relevant PRC authorities determine that we shall make supplemental social insurance and housing fund contributions or that we are subject to fines and legal sanctions in relation to our failure to make social insurance and housing fund contributions in full for our employees, our business, financial condition and results of operations may be adversely affected.

The lease agreements of our leased properties have not been registered with the relevant PRC government authorities as required by PRC law, which may expose us to potential fines.

Under PRC law, lease agreements of commodity housing tenancy are required to be registered with the local construction (real estate) departments. Although failure to do so does not in itself invalidate the leases, the parties of the lease agreements may be exposed to potential fines if they fail to rectify such non-compliance within the prescribed time frame after receiving notice from the relevant PRC government authorities. The penalty ranges from RMB1,000 to RMB10,000 for each unregistered lease, at the discretion of the relevant authority. As of the date of this annual report, the lease agreements for our leased properties in China have not been registered with the relevant PRC government authorities. As of the date of this annual report, we are not aware of any regulatory or governmental actions, claims or investigations being contemplated or any challenges by third parties to our use of our leased properties that the lease agreements of which have not been registered with the government authorities. However, we cannot assure you that the government authorities will not impose fines on us due to our failure to register any of our lease agreements, which may negatively impact our financial condition.

Any failure to comply with PRC regulations regarding the registration requirements for employee stock incentive plans may subject the PRC plan participants or us to fines and other legal or administrative sanctions.

In February 2012, SAFE promulgated the Notices on Issues Concerning the Foreign Exchange Administration for Domestic Individuals Participating in Stock Incentive Plan of Overseas Publicly Listed Company, replacing earlier rules promulgated in 2007. Pursuant to these rules, PRC citizens and non-PRC citizens who reside in China for a continuous period of not less than one year who participate in any stock incentive plan of an overseas publicly listed company, subject to a few exceptions, are required to register with SAFE through a domestic qualified agent, which could be the PRC subsidiary of such overseas-listed company, and complete certain other procedures. In addition, an overseas-entrusted institution must be retained to handle matters in connection with the exercise or sale of stock options and the purchase or sale of shares and interests. We and our executive officers and other employees who are PRC citizens or who reside in the PRC for a continuous period of not less than one year and who have been granted options will be subject to these regulations. Failure to complete the SAFE registrations may subject them to fines and legal sanctions, there may be additional restrictions on the ability of them to exercise their stock options or remit proceeds gained from the sale of their stock into the PRC. We also face regulatory uncertainties that could restrict our ability to adopt incentive plans for our directors, executive officers and employees under PRC law.

We face uncertainty with respect to indirect transfers of equity interests in PRC resident enterprises by their non-PRC holding companies.

Pursuant to the Announcement of the State Administration of Taxation on Several Issues concerning Enterprise Income Tax on the Indirect Transfers of Property by Non-Resident Enterprises, issued by the SAT in 2015, where a non-resident enterprise indirectly transfers equities and other property of a Chinese resident enterprise to evade its obligation of paying enterprise income tax by implementing arrangements that are not for bona fide commercial purpose, such indirect transfer shall, in accordance with the provisions of Article 47 of the Enterprise Income Tax Law, be re-identified and recognized as a direct transfer of equities and other property of the Chinese resident enterprise.

On February 3, 2015, the SAT issued the Announcement of the State Administration of Taxation on Several Issues Concerning the Enterprise Income Tax on Indirect Property Transfer by Non-Resident Enterprises, or SAT Bulletin 7. SAT Bulletin 7 supersedes the rules with respect to the Indirect Transfer under SAT Circular 698. SAT Bulletin 7 has introduced a new tax regime that is significantly different from the previous one under SAT Circular 698. SAT Bulletin 7 extends the PRC's tax jurisdiction to not only Indirect Transfers set forth under SAT Circular 698 but also transactions involving a transfer of other taxable assets through an offshore transfer of a foreign intermediate holding company. In addition, SAT Bulletin 7 provides clearer criteria than SAT Circular 698 for assessment of reasonable commercial purposes and has introduced safe harbors for internal group restructurings and the purchase and sale of equity through a public securities market. SAT Bulletin 7 also brings challenges to both foreign transferor and transferee (or another person who is obligated to pay for the transfer) of taxable assets. Where a non-resident enterprise transfers taxable assets indirectly by disposing of the equity interests of an overseas holding company, which is an Indirect Transfer, the non-resident enterprise, being the transferor, or the transferee, or the PRC entity that directly owns the taxable assets, may report such Indirect Transfer to the relevant tax authority. Using a "substance over form" principle, the PRC tax authority may disregard the existence of the overseas holding company if it lacks a reasonable commercial purpose and was established for the purpose of reducing, avoiding or deferring PRC tax. As a result, gains derived from such Indirect Transfer may be subject to PRC enterprise income tax, and the transferee or another person who is obligated to pay for the transfer is obligated to withhold the applicable taxes, currently at a rate of 10% for the transfer of equity interests in a PRC resident enterprise. Both the transferor and the transferee may be subject to penalties under PRC tax laws if the transferee fails to withhold the taxes and the transferor fails to pay the taxes.

On October 17, 2017, the SAT issued the Announcement of the State Administration of Taxation on Matters Concerning Withholding of Income Tax of Non-resident Enterprises at Source, or SAT Bulletin 37, which, among others, repealed the SAT Circular 698 on December 1, 2017. SAT Bulletin 37 further details and clarifies the tax withholding methods in respect of income of non-resident enterprises under SAT Circular 698. In addition, certain rules stipulated in SAT Bulletin 7 are replaced by SAT Bulletin 37. Where the non-resident enterprise fails to declare the tax payable pursuant to Article 39 of the PRC Enterprise Income Tax Law, the tax authority may order it to pay the tax due within required time limits, and the non-resident enterprise shall declare and pay the tax payable within such time limits specified by the tax authority; however, if the non-resident enterprise voluntarily declares and pays the tax payable before the tax authority orders it to do so within required time limits, it shall be deemed that such enterprise has paid the tax in time.

We face uncertainties as to the reporting and other implications of certain past and future transactions where PRC taxable assets are involved, such as offshore restructuring, sale of the shares in our offshore subsidiaries and investments. Our company may be subject to filing obligations or taxed if our company is a transferor in such transactions, and may be subject to withholding obligations if our company is a transferee in such transactions, under SAT Bulletin 7 and SAT Bulletin 37. For transfer of shares in our company by investors who are non-PRC resident enterprises, our PRC subsidiary may be requested to assist in the filing under SAT Bulletin 7 and SAT Bulletin 37. As a result, we may be required to expend valuable resources to comply with SAT Bulletin 7 and SAT Bulletin 37 or to request the relevant transferors from whom we purchase taxable assets to comply with these circulars, or to establish that our company should not be taxed under these circulars, which may have a material adverse effect on our financial condition and results of operations.

If our preferential tax treatments are revoked, become unavailable or if the calculation of our tax liability is challenged by the PRC tax authorities, we may be required to pay tax, interest and penalties in excess of our tax provisions, and our results of operations could be materially and adversely affected.

The Chinese government has provided various tax incentives to our subsidiaries in China. These incentives include reduced enterprise income tax rates. For example, under the Enterprise Income Tax Law and its implementation rules, the statutory enterprise income tax rate is 25%. However, the income tax of an enterprise that has been determined to be a technologically advanced service enterprise can be reduced to a preferential rate of 15%. Any increase in the enterprise income tax rate applicable to our PRC subsidiary, or any discontinuation or retroactive or future reduction of any of the preferential tax treatments currently enjoyed by our PRC subsidiary, could adversely affect our business, financial condition and results of operations. In addition, in the ordinary course of our business, we are subject to complex income tax and other tax regulations and significant judgment is required in the determination of a provision for income taxes. Although we believe our tax provisions are reasonable, if the PRC tax authorities successfully challenge our position and we are required to pay tax, interest and penalties in excess of our tax provisions, our financial condition and results of operations would be materially and adversely affected.

Certain PRC regulations may make it more difficult for us to pursue growth through acquisitions.

Among other things, the Regulations on Mergers and Acquisitions of Domestic Enterprises by Foreign Investors, or the M&A Rules, adopted by six PRC regulatory agencies in 2006 and amended in 2009, established additional procedures and requirements that could make merger and acquisition activities by foreign investors more time-consuming and complex. Such regulation requires, among other things, the MOFCOM be notified in advance or its approval be obtained in certain situations, such as any change-of-control transaction in which a foreign investor acquires control of a PRC domestic enterprise of Undertakings, issued by the State Council in 2008 and amended in 2018, were triggered. Moreover, the Anti-Monopoly Law promulgated by the Standing Committee of the PRC National People's Congress, or NPC, which was lastesd revised in June 2022 and came into effect in August 2022, requires that transactions which are deemed concentrations and involve parties with specified turnover thresholds must be cleared by the State Council's anti-monopoly law enforcement authority before they can be completed. In addition, PRC national security review rules which became effective in September 2011 require acquisitions by foreign investors of PRC companies engaged in military-related or certain other industries that are crucial to national security be subject to security review before consummation of any such acquisition. We may pursue potential strategic acquisitions that are complementary to our business and operations. Complying with the requirements of these regulations to complete such transactions could be time-consuming, and any required approval processes, including obtaining approval or clearance from the State Council's anti-monopoly law enforcement authority, may delay or inhibit our ability to complete such transactions, which could affect our ability to expand our business or maintain our market share.

PRC regulations relating to offshore investment activities by PRC residents may limit our PRC subsidiaries' ability to change their registered capital or distribute profits to us or otherwise expose us or our PRC resident beneficial owners to liability and penalties under PRC laws.

In July 2014, SAFE promulgated the Circular on Relevant Issues Concerning Foreign Exchange Control on Domestic Residents' Offshore Investment and Financing and Roundtrip Investment Through Special Purpose Vehicles, or SAFE Circular 37. SAFE Circular 37 requires PRC residents (including PRC individuals and PRC corporate entities as well as foreign individuals that are deemed as PRC residents for foreign exchange administration purpose) to register with SAFE or its local branches in connection with their direct or indirect offshore investment activities. SAFE Circular 37 is applicable to our shareholders who are PRC residents and may be applicable to any offshore acquisitions that we make in the future.

Under SAFE Circular 37, PRC residents who make, or have prior to the implementation of SAFE Circular 37 made, direct or indirect investments in offshore special purpose vehicles, or SPVs, will be required to register such investments with SAFE or its local branches. In addition, any PRC resident who is a direct or indirect shareholder of an SPV, is required to update its filed registration with the local branch of SAFE with respect to that SPV, to reflect any material change, including, among other things, any major change of a PRC resident shareholder, name or term of operation of the SPVs, or any increase or reduction of the SPVs' registered capital, share transfer or swap, merger or division. Moreover, any subsidiary of such SPV in China is required to urge the PRC resident shareholders to update their registration with the local branch of SAFE. If any PRC shareholder of such SPV fails to make the required registration or to update the previously filed registration, the subsidiary of such SPV in China may be prohibited from distributing its profits or the proceeds from any capital reduction, share transfer or liquidation to the SPV, and the SPV may also be prohibited from making additional capital contributions into its subsidiary in China. On February 13, 2015, SAFE promulgated a Notice on Further Simplifying and Improving Foreign Exchange Administration Policy on Direct Investment, or SAFE Notice 13, which became effective on June 1, 2015. Under SAFE Notice 13, applications for foreign exchange registration of inbound foreign direct investments and outbound overseas direct investments, including those required under SAFE Circular 37, will be filed with qualified banks instead of SAFE or its branches. The qualified banks will directly examine the applications and accept registrations under the supervision of SAFE.

Some of our existing shareholders, each of whom owns our ordinary shares, including but not limited to as a result of exercising share options, are PRC residents under SAFE Circular 37. However, we cannot provide any assurance that these PRC residents comply with our request to make or obtain any applicable registrations or change registration or comply with all of the requirements under SAFE Circular 37 or other related rules. Furthermore, we may not be informed of the identities of all the PRC residents holding direct or indirect interest in our company. The failure or inability of our PRC resident shareholders to comply with the registration procedures set forth in these regulations may subject us to fines and legal sanctions, restrict our cross-border investment activities, limit the ability of our wholly foreign-owned subsidiary in China to distribute dividends and the proceeds from any reduction in capital, share transfer or liquidation to us, and we may also be prohibited from injecting additional capital into the subsidiary. Moreover, failure to comply with the various foreign exchange registration requirements described above could result in liability under PRC law for circumventing applicable foreign exchange restrictions. As a result, our business operations and our ability to distribute profits to you could be materially and adversely affected.

Furthermore, the interpretation and implementation of these foreign exchange regulations has been constantly evolving, it is unclear how these regulations, and any future regulation concerning offshore or cross-border transactions, will be interpreted, amended and implemented by the relevant government authorities. For example, we may be subject to a more stringent review and approval process with respect to our foreign exchange activities, such as remittance of dividends and foreign-currency-denominated borrowings, which may adversely affect our financial condition and results of operations. In addition, if we decide to acquire a PRC domestic company, we cannot assure you that we or the owners of such company, as the case may be, will be able to obtain the necessary approvals or complete the necessary filings and registrations required by the foreign exchange regulations. This may restrict our ability to implement our acquisition strategy and could adversely affect our business and prospects.

We may be materially adversely affected if our shareholders and beneficial owners who are PRC entities fail to comply with the relevant PRC overseas investment regulations.

On December 26, 2017, the NDRC promulgated the Administrative Measures on Overseas Investments, or NDRC Order No. 11, which took effect as of March 1, 2018. According to NDRC Order No. 11, non-sensitive overseas investment projects are subject to record-filing requirements with the local branch of the NDRC. On September 6, 2014, MOFCOM promulgated the *Administrative Measures on Overseas Investments*, which took effect as of October 6, 2014. According to this regulation, overseas investments of PRC enterprises that involve non-sensitive countries and regions and non-sensitive industries are subject to record-filing requirements with a local MOFCOM branch. According to the *Circular of the State Administration of Foreign Exchange on Issuing the Regulations on Foreign Exchange Administration of the Overseas Direct Investment of Domestic Institutions*, which was promulgated by SAFE on July 13, 2009 and took effect on August 1, 2009, PRC enterprises must register for overseas direct investment with a local SAFE branch.

We may not be fully informed of the identities of all our shareholders or beneficial owners who are PRC entities, and we cannot provide any assurance that all of our shareholders and beneficial owners who are PRC entities has or will comply with our request to complete the overseas direct investment procedures under the aforementioned regulations or other related rules in a timely manner, or at all. If they fail to complete the filings or registrations required by the overseas direct investment regulations, the relevant authorities may order them to suspend or cease the implementation of such investment impose warnings and sanctions and make corrections within a specified time, or limit our ability to distribute dividends and proceeds to our PRC subsidiary, which may adversely affect our business, financial condition and results of operations.

PRC regulation of loans to and direct investment in PRC entities by offshore holding companies and governmental control of currency conversion may delay or prevent us from using the proceeds of our initial public offering to make loans or additional capital contributions to our PRC subsidiary, which could materially and adversely affect our liquidity and our ability to fund and expand our business.

We are an offshore holding company conducting our operations in China through our PRC subsidiary. We also hold certain intellectual properties and outsource certain research and development activities related to these intellectual properties to our subsidiaries. We may in the future make loans or provide guarantee to our PRC subsidiary subject to the approval or registration from governmental authorities and limitation of amount, or we may make additional capital contributions to our wholly foreign-owned subsidiary in China. Any loans to our wholly foreign-owned subsidiary in China, which are treated as foreign-invested enterprises under PRC law, are subject to foreign exchange loan registrations. In addition, a foreign-invested enterprise, or FIE, shall use its capital pursuant to the principle of authenticity and self-use within its business scope. The capital of an FIE shall not be used for the following purposes: (i) directly or indirectly used for payment beyond the business scope of the enterprises or the payment prohibited by relevant laws and regulations; (ii) directly or indirectly used for investment in securities or investments other than banks' principal-secured products unless otherwise provided by relevant laws and regulations; (iii) the granting of loans to non-affiliated enterprises, except where it is expressly permitted in the business license; and (iv) paying the expenses related to the purchase of real estate that is not for self-use (except for the foreign-invested real estate enterprises).

In light of the various requirements imposed by PRC regulations on loans to and direct investment in PRC entities by offshore holding companies, we cannot assure you that we will be able to complete the necessary government registrations or obtain the necessary government approvals on a timely basis, if at all, with respect to future loans by us to our PRC subsidiary or with respect to future capital contributions by us to our PRC subsidiary. If we fail to complete such registrations or obtain such approvals, our ability to use the proceeds from our initial public offering and to capitalize or otherwise fund our PRC operations may be negatively affected, which could materially and adversely affect our liquidity and our ability to fund and expand our business.

We may rely on dividends and other distributions on equity paid by our PRC subsidiary to fund any cash and financing requirements we may have, and any limitation on the ability of our PRC subsidiary to make payments to us could have a material and adverse effect on our ability to conduct our business.

We are a Cayman Islands holding company and we currently rely principally on equity financing for our cash requirements, including the funds necessary to pay cash considerations for services we may incur. In the future, when and after we become profitable and generate cash flows from operating activities, we may rely principally on dividends and other distributions on equity from our PRC and U.S. subsidiaries for our cash requirements, including the funds necessary to pay dividends and other cash distributions to our shareholders for services of any debt we may incur. If our PRC subsidiary incurs debt on its own behalf in the future, the instruments governing the debt may restrict its ability to pay dividends or make other distributions to us. Under PRC laws and regulations, our PRC subsidiary, which is a wholly foreign-owned enterprise, may pay dividends only out of its respective accumulated profits as determined in accordance with PRC accounting standards and regulations. In addition, a wholly foreign-owned enterprise is required to set aside at least 10% of its accumulated after-tax profits each year, if any, to fund a certain statutory reserve fund, until the aggregate amount of such fund reaches 50% of its registered capital. Such reserve funds cannot be distributed to us as dividends. At its discretion, a wholly foreign-owned enterprise may allocate a portion of its after-tax profits based on PRC accounting standards to an enterprise expansion fund, or a staff welfare and bonus fund.

A portion of our revenue was generated by our PRC subsidiary in Renminbi, which is not freely convertible into other currencies. As a result, any restriction on currency exchange may limit the ability of our PRC subsidiary to use its Renminbi revenues to pay dividends to us.

The PRC government may continue to strengthen its capital controls, and more restrictions and substantial vetting process may be put forward by SAFE for cross-border transactions falling under both the current account and the capital account. Any limitation on the ability of our PRC subsidiary to pay dividends or make other kinds of payments to us could materially and adversely limit our ability to grow, make investments or acquisitions that could be beneficial to our business, pay dividends, or otherwise fund and conduct our business.

In addition, the Enterprise Income Tax Law and its implementation rules provide that a withholding tax rate of up to 10% will be applicable to dividends payable by Chinese companies to non-PRC-resident enterprises unless otherwise exempted or reduced according to treaties or arrangements between the PRC central government and governments of other countries or regions where the non-PRC-resident enterprises are incorporated.

Fluctuations in exchange rates could have a material adverse effect on our results of operations and the value of your investment.

The value of the Renminbi against the U.S. dollar and other currencies may fluctuate and is affected by, among other things, changes in political and economic conditions in China and by China's foreign exchange policies. On July 21, 2005, the PRC government changed its policy of pegging the value of the Renminbi to the U.S. dollar, and the Renminbi appreciated more than 20% against the U.S. dollar over the following three years. Between July 2008 and June 2010, this appreciation halted and the exchange rate between the Renminbi and the U.S. dollar remained within a narrow band. Since June 2010, the Renminbi has fluctuated against the U.S. dollar, at times significantly and unpredictably. Since October 1, 2016, Renminbi has joined the International Monetary Fund's basket of currencies that make up the Special Drawing Right, or SDR, along with the U.S. dollar, the Euro, the Japanese yen and the British pound. In the fourth quarter of 2016, the Renminbi has depreciated significantly in the backdrop of a surging U.S. dollar and persistent capital outflows of China. With the development of the foreign exchange market and progress towards interest rate liberalization and Renminbi internationalization, the PRC government may in the future announce further changes to the exchange rate system, and we cannot assure you that the Renminbi will not appreciate or depreciate significantly in value against the U.S. dollar in the future. It is difficult to predict how market forces or PRC or U.S. government policy may impact the exchange rate between the Renminbi and the U.S. dollar in the future.

Significant revaluation of the Renminbi may have a material and adverse effect on your investment. For example, to the extent that we need to convert U.S. dollars we received from our equity financings into Renminbi for our operations, appreciation of the Renminbi against the U.S. dollar would have an adverse effect on the Renminbi amount we would receive from the conversion. Conversely, if we decide to convert our Renminbi into U.S. dollars for the purpose of making payments for dividends on our ordinary shares or the ADSs or for other business purposes, appreciation of the U.S. dollar against the Renminbi would have a negative effect on the U.S. dollar amount available to us.

Very limited hedging options are available in China to reduce our exposure to exchange rate fluctuations. To date, we have not entered into any hedging transactions in an effort to reduce our exposure to foreign currency exchange risk. While we may decide to enter into hedging transactions in the future, the availability and effectiveness of these hedges may be limited and we may not be able to adequately hedge our exposure or at all. In addition, our currency exchange losses may be magnified by PRC exchange control regulations that restrict our ability to convert Renminbi into foreign currency.

Governmental control of currency conversion may limit our ability to utilize our cash balance effectively and affect the value of your investment.

The PRC government imposes controls on the convertibility of the Renminbi into foreign currencies and, in certain cases, the remittance of currency out of China. We did not receive any of our revenues in Renminbi in cash in the years ended Decemebr 31, 2020, 2021 and 2022. Under our current corporate structure, our Cayman Islands holding company primarily relies on proceeds from previous equity financing activities to fund any cash and financing requirements we may have. Under existing PRC foreign exchange regulations, payments of current account items, including profit distributions, interest payments and trade and service-related foreign exchange transactions, can be made in foreign currencies without prior approval of SAFE by complying with applicable laws and regulations, as well as certain procedural requirements. Specifically, under the existing exchange restrictions, without prior approval of SAFE, cash generated from the operations of our PRC subsidiary may be used to pay dividends to our company. However, approval from or registration with appropriate government authorities is required where Renminbi is to be converted into foreign currency and remitted out of China to pay capital expenses such as the repayment of loans denominated in foreign currencies. As a result, we need to obtain SAFE approval to use the cash generated from the operations of our PRC subsidiary to pay off their respective debt in a currency other than Renminbi owed to entities outside China, or to make other capital expenditure payments outside China in a currency other than Renminbi. The PRC government may at its discretion restrict access to foreign currencies for current account transactions in the future. If the foreign exchange control system prevents us from obtaining sufficient foreign currencies to satisfy our foreign currency demands, we may not be able to pay dividends in foreign currencies to our shareholders, including holders of the ADSs.

Risks Related to Our Financial Prospects and Need for Additional Capital

We have a limited operating history, which may make it difficult to evaluate our current business and predict our future performance.

We are a clinical stage biotechnology company with a limited operating history. Since our inception in 2011, we have focused substantially all of our efforts and financial resources on the discovery and development of antibody therapeutics for the treatment of cancer. We have no products approved for commercial sale and therefore we have not generated any revenue from product sales. We have not obtained regulatory approvals for any of our product candidates and there is no assurance that we will obtain approvals in the future. We expect to continue to incur significant expenses and operating losses over the next several years and for the foreseeable future. Our prior losses, combined with expected future losses, have had and may continue to have an adverse effect on our working capital.

Our operations to date have focused on developing our product candidates, building our intellectual property portfolio, conducting preclinical testing and clinical trials, and raising capital. These operations provide a limited basis for you to assess our ability to successfully market and commercialize our product candidates. Consequently, predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history. We will encounter risks and difficulties frequently experienced by early-stage companies in rapidly evolving fields as we seek to shift our focus to late stage development and commercial activities. If we do not address these risks and difficulties successfully, we may not be successful in such a transition.

We have incurred net losses historically and we may continue to incur net losses in the near future.

Since our inception in 2011, we have devoted our resources to the development of innovative antibodies in the therapeutic area. While we have generated revenues from licensing and collaboration deals, we have not generated any revenue from commercial product sales to date, and we have had significant operating losses since our inception. For the years ended December 31, 2020, 2021 and 2022, we incurred net losses of US$42.4 million, US$73.2 million and US$80.0 million, respectively. Substantially all of our operating losses have resulted from costs incurred in connection with our research and development programs. To date, we have financed our operations principally through proceeds from our prior equity financing activities. Our product candidates and programs are in preclinical development or early stage clinical development, and we have not received marketing approval for any of our product candidates. Our product candidates will require substantial investments and significant marketing efforts before we generate any revenues from product sales, if ever. We expect our net losses will increase as more product candidates enter into clinical trial stage. Our ability to generate product revenue and achieve profitability depends on, among other things:

- completing research and development of our product candidates;

- initiating, enrolling patients in and completing clinical trials of product candidates on a timely basis;
- obtaining regulatory approvals and marketing authorizations for any product candidates for which we complete clinical trials;
- developing and maintaining adequate manufacturing capabilities either by ourselves or in connection with third-party manufacturers;
- launching and commercializing any product candidates for which we obtain regulatory approvals and marketing authorizations;
- establishing a sales, marketing and commercialization team for any future products for which we may obtain regulatory approval;
- seeking to identify additional product candidates;
- addressing any competing technological and market developments; and
- maintaining, protecting and expanding our portfolio of intellectual property rights.

We may never succeed in these activities and, even if we do, may never generate revenue that is significant enough to achieve profitability. Because of the numerous risks and uncertainties associated with the development, delivery and commercialization of complex innovative antibody therapeutic, we are unable to accurately predict the timing or amount of expenses or when, or if, we will be able to achieve profitability. If we are required by regulatory authorities to perform studies in addition to those currently expected, or if there are any delays in the initiation and completion of our clinical trials or the development of any of our product candidates, our expenses could increase and profitability could be further delayed.

If we fail to become profitable or are unable to sustain profitability on a continuing basis, we may be unable to continue our operations at planned levels and be forced to reduce our operations. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become or remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business or continue our operations. Failure to become and remain profitable may adversely affect the market price of the ADSs and our ability to raise capital and continue operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We may need to obtain substantial additional financing to fund our growth and operations, which may not be available on acceptable terms, if at all.

The development of biopharmaceutical product candidates is capital-intensive. We have used substantial funds to advance our discovery programs and develop our technology and product candidates, and will require significant funds to conduct further research and development, preclinical testing and clinical trials of our product candidates, to seek regulatory approvals for our product candidates and to manufacture and market products, if any, that are approved for commercial sales. If our product candidates enter and advance through preclinical studies and clinical trials, we will need substantial additional funds to expand our development, regulatory and manufacturing capabilities. We also expect to incur significant costs associated with operating as a public company.

- To date, we have funded our operations primarily through capital contributions from our shareholders via private placements and proceeds from our initial public offering. Our operations have consumed substantial amounts of cash since inception. As of December 31, 2022, we had US$143.8 million in cash and cash equivalents. The net cash used in our operating activities was US$28.5 million, US$43.4 million and US$48.6 million for the years ended December 31, 2020, 2021 and 2022, respectively. Our future funding requirements and the period for which we expect increasing capital need may be different from what we plan. Our monthly spending levels vary based on new and ongoing research and development activities. Because of the numerous risks and uncertainties associated with our product development, we are unable to accurately predict the timing and amount of our operating expenditures, which will depend largely on:

- the scope, timing, progress, costs and results of discovery, preclinical development, laboratory testing and clinical development activities of our current product candidates;
- the number, scope, progress and results of preclinical and clinical programs we decide to pursue;
- the progress of the development efforts of parties with whom we have entered or may in the future enter into collaborations and research and development agreements;
- our ability to maintain our current licenses, research and development programs, and to establish new collaboration arrangements;
- our ability to maintain competitive advantage over other AI-powered technology platforms at generating highly differentiated product candidates.
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the cost, timing and outcome of regulatory review of any of our product candidates;
- the costs and timing of future commercialization activities, including manufacturing, marketing, sales, and distribution, for any of our product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval; and
- our efforts to enhance operational systems and hire additional personnel, including personnel to support development of our product candidates and satisfy our obligations as a public company.

We will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. Any additional capital-raising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our current and future product candidates, if approved. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or altogether cease our research and development programs or future commercialization efforts.

Raising additional capital may lead to dilution of shareholdings by our existing shareholders and restrict our operations or require us to relinquish rights to our technologies or product candidates.

We may seek additional funding through a combination of equity and debt financings and collaborations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the beneficial ownership interest of existing holders of our shares and/or ADSs will be diluted, and the terms may include liquidation or other preferences that adversely affect the rights of existing holders of our shares and/or ADSs.

The incurrence of additional indebtedness or the issuance of certain equity securities could result in increased fixed payment obligations and could also result in certain additional restrictive covenants, such as incurring additional debt, making capital expenditures, or declaring dividends. If we raise additional funds through partnerships, collaborations, strategic alliances, or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, product candidates, or future revenue streams, or grant licenses on terms that are not favorable to us.

We have certain shareholders who have board representation rights and their individual interests may differ from yours.

In 2014, we completed private placements of our Series A-1 and A-2 preferred shares, in which we raised gross proceeds of approximately US$8.5 million. In 2016, we completed a private placement of our Series B preferred shares, in which we raised gross proceeds of approximately US$28.0 million. In 2018, we completed a private placement of our Series C-1 preferred shares, in which we raised gross proceeds of approximately US$50.0 million. In 2019, we completed private placements of our Series C-2 and C-3 preferred shares, in which we raised gross proceeds of approximately US$69.0 million in aggregate. As a result of these private placements, a significant portion of our outstanding equity is currently held by multiple separate institutional investors through several separate funds and our founders.

These institutional investors will continue have a significant level of influence because of their level of ownership, including a greater ability than you and our other shareholders to influence the election of directors and the potential outcome of matters submitted to a vote of our shareholders, such as mergers, the sale of substantially all of our assets and other extraordinary corporate matters. These investors and our founder, Peter Luo, also have certain rights, such as board representation right and registration right that our other shareholders do not have.

For instance, our current effective memorandum and articles of association provides that JSR Limited shall have the right to designate, appoint, remove and replace and reappoint one director so long it holds at least five percent of the shares outstanding on a fully-diluted basis and an as-converted basis, although JSR Limited currently does not have representation at our board; as long as Wuxi Pharmatech Healthcare Fund I L.P., which is controlled by the ultimate controlling party of our sole supplier, holds at least five percent of the shares outstanding on a fully-diluted basis, it shall have the right to nominate one independent non-executive director and such one director shall be appointed and agreed by the board; as long as Peter Luo holds or beneficially owns any shares or is employed by us or any of our subsidiaries, he will serve as one of our directors and the Chairman of the Board of Directors; in addition, during the period commencing upon February 2021 and ending on the earlier of (i) the date upon which Peter Luo beneficially owns less than five percent of the shares outstanding on a fully diluted basis, (ii) the death or legal determination of Peter Luo's incapacity or (iii) the termination of Peter Luo as an executive officer or principal scientific advisor to us or any of our subsidiaries or for cause (as determined under his related employment or consulting arrangements and subject to all related cure provisions), Peter Luo shall have the right to designate, appoint, remove and replace and reappoint one additional director; and as long as General Atlantic Singapore AI Pte. Ltd. and its affiliates hold at least five percent of the shares outstanding on a fully-diluted basis, they shall have the right to designate, appoint, remove and replace and reappoint one director.

The interests of these investors could conflict with the interests of our other shareholders, including you, and any future transfer by these investors of their shares of preferred or ordinary share to other investors who have different business objectives could have a material adverse effect on our business, results of operations, financial condition and the market value of our ordinary shares or ADSs.

Risks Related to Clinical Development of Our Product Candidates

We may not be able to identify or discover new product candidates, and may allocate our limited resources to pursue a particular product candidate and fail to capitalize on product candidates that may later prove to be more profitable, or for which there is a greater likelihood of success.

Although we will focus our efforts on continued preclinical and clinical developments, regulatory approval process and commercialization with respect to our existing product candidates, the success of our business depends in part upon our ability to identify, license, discover, develop, or commercialize additional product candidates. Research programs to identify new product candidates require substantial technical, financial, and human resources. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- our research or business development methodology or search criteria and process may be unsuccessful in identifying potential product candidates;
- our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to obtain marketing approval; and

- potential product candidates may not be effective in treating their targeted diseases.

Because we have limited financial and managerial resources, we focus on research programs and product candidates for specific targets. As a result, we may forgo or delay pursuit of opportunities with other product candidates that later may be proved to have greater commercial potential or a greater likelihood of success. On the other hand, if we do not prioritize the allocation of our resources and conduct research programs that cover a broad range of targets or engage clinical programs that are overly expansive, we may be subject to significant risk of loss as a large part of the research and clinical programs fail. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities.

Accordingly, there can be no assurance that we will ever be able to develop suitable potential product candidates through internal research programs, which could materially adversely affect our future growth and prospects.

We may not be successful in our efforts to use and expand our proprietary platforms to build a pipeline of product candidates.

A key element of our strategy is to leverage our technology platform to expand our pipeline of antibody product candidates and in order to do so, we will continue to invest in our platform and development capabilities. Although our research and development efforts to date have resulted in a pipeline of product candidates, these product candidates may not be safe and effective. In addition, although we expect that our platform will allow us to develop a diverse pipeline of novel and differentiated product candidates, we may not prove to be successful at doing so. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects, efficacy or other characteristics that indicate that they are unlikely to be products that will receive marketing approval or achieve market acceptance. Even after approval, if we cannot successfully develop or commercialize our products, or if serious adverse events are discovered after commercialization, we will not be able to generate any product revenue, which would adversely affect business.

Any failures or setbacks in our platforms or our other proprietary technologies could negatively affect our business and financial condition.

Our product candidates are created with, and dependent upon, our proprietary antibody discovery platforms, such as our proprietary Dynamic Precision Library platform, which includes our NEObody platform, SAFEbody platform and POWERbody platform. These proprietary technology platforms are also the basis of our collaborations with certain other partners. To date, no products based on any of these technologies have been approved for commercial sale in any jurisdiction. Any failures or setbacks with respect to our proprietary technologies, including adverse effects resulting from the use of product candidates derived from these technologies in human clinical trials and/or the imposition of clinical holds on trials of any product candidates using our proprietary technologies, could have a detrimental impact on our clinical pipeline, as well as our ability to maintain and enter into new corporate collaborations regarding our technologies or otherwise, which would negatively affect our business and financial conditions.

Our product candidates, for which we intend to seek approval as biologic products, may face competition sooner than anticipated.

Even if we are successful in achieving a final regulatory approval to commercialize a product candidate ahead of our competitors, our product candidates may face competition from biosimilar or other biologic products. In the United States, our product candidates are regulated by the FDA as biologic products and we intend to seek approval for these product candidates pursuant to the Biologics License Application (BLA) pathway. The Biologics Price Competition and Innovation Act of 2009 (BPCIA) created an abbreviated pathway for the approval of biosimilar and interchangeable biologic products. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as “interchangeable” based on its similarity to an existing brand product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product was approved under a BLA. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. A product may also make modifications and seek approval as a BLA. While it is uncertain when such processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our product candidates.

There is a risk that any of our product candidates approved as a biological product under a BLA would not qualify for the 12-year period of exclusivity or that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for interchangeable or generic competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are not fully understood.

Jurisdictions in addition to the United States have established abbreviated pathways for regulatory approval of biological products that are biosimilar to earlier approved reference products. For example, the European Union has had an established regulatory pathway for biosimilars since 2005.

The increased likelihood of biosimilar competition has increased the risk of loss of innovators' market exclusivity. Due to this risk, and uncertainties regarding patent protection, if our clinical candidates are approved for marketing, it is not possible to predict the length of market exclusivity for any particular product with certainty based solely on the expiration of the relevant patent(s) or the current forms of regulatory exclusivity. It is also not possible to predict changes in United States regulatory law that might reduce biological product regulatory exclusivity. The loss of market exclusivity for a product would likely materially and negatively affect revenues and we may not generate adequate or sufficient revenues from them or be able to reach or sustain profitability.

We depend substantially on the success of our product candidates, particularly our anti-CTLA-4 franchise, including ADG116 and ADG126, and our two anti-CD137 antibodies, ADG106 and ADG206, which are in clinical development, and our ability to identify additional product candidates. Clinical trials of our product candidates may not be successful. If we are unable to successfully identify new product candidates, complete clinical development, obtain regulatory approval and commercialize our product candidates, or experience significant delays in doing so, our business will be materially harmed.

Our business and the ability to generate revenue related to product sales, if ever, will depend on the successful development, regulatory approval and commercialization of our antibody product candidates for the treatment of patients with cancer, particularly ADG116, ADG126, ADG106 and ADG206, which are still in clinical stage. Other than our wholly-owned product candidates (ADG116, ADG126, ADG106 and ADG206) and our outlicensed product candidates, ADG104 and ADG125, our current product candidates are in relatively early stages of development. We have invested a significant portion of our efforts and financial resources in the development of our existing product candidates and all of our product candidates will require significant further development and financial resources. The success of our product candidates, including ADG116, ADG126, ADG106 and ADG206, will depend on several factors, including:

- successful enrollment in, and completion of, preclinical studies and clinical trials;
- receipt of regulatory approvals from the FDA, NMPA and other comparable regulatory authorities for our product candidates;
- establishing commercial manufacturing capabilities, either by building facilities ourselves or making arrangements with third-party manufacturers;
- relying on third parties to conduct our clinical trials safely and efficiently;
- obtaining and maintaining patent, trade secret and other intellectual property protection and regulatory exclusivity;
- protecting our rights in our intellectual property;
- ensuring we do not infringe, misappropriate or otherwise violate the patent, trade secret or other intellectual property rights of third parties;
- launching commercial sales of our product candidates, if and when approved;

- competition with other product candidates and drugs; and
- continued acceptable safety profile for our product candidates following final regulatory approval, if and when received.

Due to the uncertain, time-consuming and costly clinical development and regulatory approval process, we may not successfully develop any of our product candidates, or we or our partners may choose to discontinue the development of product candidates for a variety of reasons. Our failure to effectively advance our development programs could have a material adverse effect on our business, financial condition, results of operations and future growth prospects, and cause the market price of our ADSs to decline.

Clinical trials are expensive, time consuming and difficult to design and implement and may fail to demonstrate adequate safety and efficacy of our product candidates. The results of our current and previous preclinical studies or clinical trials may not be predictive of future results, and the results of our current and planned clinical trials may not satisfy the requirements of the FDA or comparable foreign regulatory authorities or provide the basis for regulatory approval.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct preclinical studies and extensive clinical trials to demonstrate their safety and efficacy in humans. Clinical testing is expensive and difficult to design and implement. Clinical testing can take many years to complete, and its ultimate outcome is uncertain. A failure of one or more clinical trials can occur at any stage of the process. We will be required to demonstrate with substantial evidence through well-controlled clinical trials that our product candidates are safe, pure, and effiective for use in a diverse patient population before we can seek final regulatory approvals for their commercial sale. Our clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional and expansive preclinical or clinical testings.

We cannot assure that the results of later clinical trials will replicate the results of prior clinical trials and preclinical testing. The results are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data becomes available. Product candidates in later-stage clinical trials may fail to demonstrate sufficient safety and efficacy to the satisfaction of the FDA, the NMPA and comparable foreign regulatory authorities, despite having progressed through preclinical studies or initial clinical trials. Product candidates that have shown promising results in early clinical trials may still suffer significant setbacks in subsequent clinical trials or registration clinical trials. For example, a number of companies in the biopharmaceutical industry, including those with greater resources and experience than us, have suffered significant setbacks in later staged clinical trials, even after obtaining promising results in earlier clinical trials.

A failure of a clinical trial to meet its predetermined primary endpoints may cause us to abandon a pipeline product or an indication and may delay development of any other pipeline products. Any delay in, or termination of, our clinical trials will delay the submission for regulatory approval and application, and, ultimately, our ability to commercialize any of our pipeline products and generate revenue.

Moreover, principal investigators for our clinical trials may serve and have served as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or comparable foreign regulatory authorities. The FDA or comparable foreign regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the trial. The FDA or comparable foreign regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or comparable foreign regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of our pipeline products.

We may experience delays in our ongoing clinical trials.

We may experience delays in our ongoing clinical trials, and we do not know whether planned clinical trials will begin on time, need to be redesigned, enroll patients on time, or be completed on schedule, if at all. Clinical trials can be delayed, suspended, or terminated for a variety of reasons, including the following:

- delays in or failure to obtain regulatory authorization to commence a trial;
- delays in or failure to obtain institutional review board, or IRB, approval at each site;

- delays in or failure to reach agreement on acceptable terms with prospective contract research organizations (CROs), and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- difficulty in recruiting clinical trial investigators of appropriate competencies and experience;
- delays in establishing the appropriate dosage levels in clinical trials;
- delays in or failure to recruit and enroll suitable patients to participate in a trial, particularly considering study inclusion and exclusion criteria and patients' prior lines of therapy and treatment;
- the difficulty in certain countries in identifying the sub-populations that we are trying to treat in a particular trial, which may delay enrollment and reduce the power of a clinical trial to detect statistically significant results;
- lower than anticipated retention rates of patients in clinical trials;
- failure to have patients complete a trial or return for post-treatment follow-up;
- clinical sites deviating from trial protocol or dropping out of a trial;
- delays adding new investigators or clinical trial sites;
- safety or tolerability concerns could cause us or our collaborators or governmental authorities, as applicable, to suspend or terminate a trial if it is found that the participants are being exposed to unacceptable health risks, undesirable side effects or other unfavorable characteristics of the product candidate, or if such undesirable effects or risks are found to be caused by a chemically or mechanistically similar therapeutic or therapeutic candidate;
- our third-party research contractors failing to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- changes in regulatory requirements, policies and guidelines;
- failure to comply with the applicable regulatory requirements through the clinical process;
- manufacturing sufficient quantities of a product candidate for use in clinical trials;
- he quality or stability of a product candidate falling below acceptable standards;
- changes in the treatment landscape for our target indications that may make our product candidates no longer relevant; and
- third-party actions claiming infringement by our product candidates in clinical trials outside the United States and obtaining injunctions interfering with our progress.

In addition, while we plan to submit additional investigational new drug applications, or INDs, for other product candidates, we may not be able to file such INDs on the timeline we expect. For example, we may experience manufacturing delays or other delays with IND-enabling preclinical studies. Moreover, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that suspend or terminate clinical trials. Additionally, even if such regulatory authorities agree with the design and implementation of the clinical trials set forth in an IND, we cannot guarantee that such regulatory authorities will not change their requirements in the future. These considerations also apply to new clinical trials we may submit as amendments to existing INDs.

If we are required to conduct additional clinical trials or other studies with respect to any of our product candidates beyond those that we initially contemplated, if we are unable to successfully complete our clinical trials or other studies or if the results of these studies are not positive or are only modestly positive, we may be delayed in obtaining regulatory approval for that product candidate, we may not be able to obtain regulatory approval at all or we may obtain approval for indications that are not as broad as intended. Our drug development costs will also increase if we experience delays in testing or approvals, and we may not have sufficient funding to complete the testing and approval process. Significant clinical trial delays could allow our competitors to bring drugs to market before we do and impair our ability to commercialize our drugs, if and when approved. If any of this occurs, our business will be materially harmed.

Clinical trials must be conducted in accordance with the FDA and other applicable regulatory authorities' legal requirements, regulations and guidelines, and are subject to oversight by these governmental agencies and Ethics Committees or IRBs at the medical institutions where the clinical trials are conducted. We could encounter delays if a clinical trial is suspended or terminated by us, by the IRBs or Ethics Committees of the institutions in which such trials are being conducted, by the Data Review Committee or Data Safety Monitoring Board for such trial or by the FDA, or other regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial or to perform obligations in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. If we experience delays in the completion of, or termination of, any clinical trial of our product candidates, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenues from any of these product candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process and jeopardize our ability to commence product sales and generate revenues. Significant clinical trial delays could also allow our competitors to bring products to market before we do or shorten any periods during which we have the exclusive right to commercialize our product candidates and impair our ability to commercialize our product candidates and may harm our business and results of operations.

Further, clinical trials must be conducted with supplies of our product candidates produced under current good manufacturing practices, or cGMP, requirements and other regulations. Furthermore, we rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials and while we have agreements governing their committed activities, we have limited influence over their actual performance. We depend on our collaborators and on medical institutions and CROs to conduct our clinical trials in compliance with good clinical practice, or GCP, requirements. To the extent our collaborators or the CROs fail to enroll participants for our clinical trials, fail to conduct the study in accordance with GCP or are delayed for a significant time in the execution of trials, including achieving full enrollment, we may be affected by increased costs, program delays or both, which may harm our business. In addition, clinical trials that are conducted in countries outside the United States may subject us to further delays and expenses as a result of increased shipment costs, additional regulatory requirements and the engagement of non-U.S. CROs, as well as expose us to risks associated with clinical investigators who are unknown to the FDA, and different standards of diagnosis, screening and medical care.

If we encounter difficulties in enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

Successful and timely completion of clinical trials will require that we enroll a sufficient number of patients. Our clinical trials may be subject to delays for a variety of reasons, including as a result of enrollment taking longer than anticipated, subject withdrawal or adverse events. These types of developments could cause us to delay the trial or halt further development.

While we believe our differentiated product candidates address highly unmet medical needs that will facilitate our patient enrollment, clinical trials may compete with other clinical trials that are in the same therapeutic areas as our product candidates, and this competition reduces the number and types of patients available to us, as some patients who might have opted to enroll in our trials may instead opt to enroll in a trial being conducted by one of our competitors. Moreover, enrolling patients in clinical trials for cancer therapies is challenging, as cancer patients will first receive the applicable standard of care. Many patients who respond positively to the standard of care antibody therapy (and thus do not enroll in clinical trials) are believed to have tumor types that would have responded well to our product candidates. Patients who fail to respond positively to the standard of care treatment will be eligible for clinical trials of unapproved product candidates. However, these prior treatment regimens may render our therapies less effective in clinical trials. Additionally, patients who have failed with prior approved therapies will typically have more advanced cancer and a poorer long-term prognosis.

Because the number of qualified clinical investigators and clinical trial sites is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites. We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons, including:

- severity of the disease under investigation;
- the size and nature of the patient population;
- the patient eligibility criteria defined in the protocol;
- the size of the study population required for analysis of the trial’s primary endpoints;
- perceived risks and benefits of our pipeline products;
- our resources to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the proximity of patients to trial sites;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- our ability to obtain and maintain patients’ consent; and
- the risk that patients enrolled in clinical trials will not complete a clinical trial.

These factors may make it difficult for us to enroll enough patients to complete our clinical trials in a timely and cost-effective manner. Delays in the completion of any clinical trial of our product candidates will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate revenue. In addition, some of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

Interim, topline or preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary or topline or data from our preclinical studies and clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available.

From time to time, we may also disclose interim data from our preclinical studies and clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects. Further, disclosure of interim data by us or by our competitors could result in volatility in the price of our common stock.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions, or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. If the interim, topline, or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects, or financial condition.

Risks Related to Obtaining Regulatory Approval of Our Drug Candidates

The regulatory approval processes of the FDA, NMPA and other comparable regulatory authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approvals for our product candidates, our business will be substantially harmed.

In the United States, marketing approval of biologics requires the submission of a BLA to the FDA, and we are not permitted to market any product candidate in the United States until we obtain approval from the FDA of the BLA for that product candidate. A BLA must be supported by extensive clinical and preclinical data, as well as extensive information regarding pharmacology, chemistry, manufacturing and controls. Outside the United States, many comparable foreign regulatory authorities employ similar approval processes.

We have not previously submitted a BLA to the FDA or similar regulatory approval filings to the NMPA or other comparable foreign authorities, for any product candidate, and we cannot be certain that any of our product candidates will receive regulatory approval. Obtaining approval of a BLA can be a lengthy, expensive and uncertain process, and as a company we have no experience with the preparation of a BLA submission or any other application for marketing approval. In addition, the FDA has the authority to require a risk evaluation and mitigation strategies, or REMS, plan as part of a BLA or after approval, which may impose further requirements or restrictions on the distribution or use of an approved biologic, such as limiting prescribing to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients who meet certain safe-use criteria and requiring treated patients to enroll in a registry.

FDA approval is not guaranteed, and the time required to obtain approval by the FDA, NMPA and other comparable regulatory authorities is unpredictable but typically takes many years following the commencement of preclinical trials and clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, due to external issues such as pandemics or other public health emergencies, FDA, NMPA and other comparable regulatory authorities may be delayed in their review of product applications. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate, and it is possible that none of our existing product candidates or any product candidates we may discover, in-license or acquire and seek to develop in the future will ever obtain regulatory approval.

Our product candidates could fail to receive regulatory approval from the FDA, NMPA or a comparable regulatory authority for many reasons, including:

- disagreement with the design or implementation of our clinical trials;
- failure to demonstrate that a product candidate is safe and effective or safe, pure, and potent for its proposed indication;
- failure of clinical trial results to meet the level of statistical significance required for approval;
- failure to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- disagreement with our interpretation of data from preclinical trials or clinical trials;
- the insufficiency of data collected from clinical trials of our product candidates to support the submission and filing of a BLA or other submission or to obtain regulatory approval;
- the FDA, NMPA or comparable regulatory authority's finding of deficiencies related to the manufacturing processes;
- failure of our product candidates to ensure compliance with Good Manufacturing Practice, or cGMP, following inspections during the regulatory review process or across the production cycle of our product; and
- changes in approval policies, guidances or regulations that render our preclinical and clinical data insufficient for approval.

The FDA and other regulatory authorities have substantial discretion in the approval process, and determining when or whether regulatory approval will be obtained for any of our product candidates. For example, regulatory authorities in various jurisdictions have in the past had, and may in the future have, differing requirements for, interpretations of and opinions on our preclinical and clinical data. As a result, we may be required to conduct additional preclinical studies, alter our proposed clinical trial designs or conduct additional clinical trials to satisfy the regulatory authorities in each of the jurisdictions in which we hope to conduct clinical trials and develop and market our products, if approved. Further, even if we believe the data collected from clinical trials of our product candidates are promising, such data may not be sufficient to support approval by the FDA or any other regulatory authority.

The FDA, NMPA or a comparable regulatory authority may require more information, including additional preclinical or clinical data, to support approval, which may delay or prevent approval and our commercialization plans, or we may decide to abandon the development program. If we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may grant approval contingent on the performance of costly post-marketing clinical trials, may approve a product candidate with a label that is not desirable for the successful commercialization of that product candidate, or may be difficult to meet manufacturing requirements. In addition, if our product candidate produces undesirable side effects or safety issues, the FDA may require the establishment of Risk Evaluation Mitigation Strategies, or REMS, or the NMPA or a comparable regulatory authority may require the establishment of a similar strategy, that may, for instance, restrict distribution of our drugs and impose burdensome implementation requirements on us. Any of the foregoing scenarios could materially harm the commercial prospects of our product candidates.

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved or commercialized in a timely manner or at all, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory, and policy changes, the FDA's ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the FDA have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies may also slow the time necessary for new biologics or modifications to licensed biologics to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities.

Separately, in response to the COVID-19 pandemic, on March 10, 2020, the FDA announced its intention to postpone most inspections of foreign manufacturing facilities, and on March 18, 2020, the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, on July 10, 2020, the FDA announced its intention to resume certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. On February 2, 2022, the FDA announced it would be resuming domestic surveillance inspections across all product types, beginning on February 7, 2022, in light of declining COVID-19 rates. Regulatory authorities outside the United States may adopt or lift similar restrictions or other policy measures in response to the COVID-19 pandemic. While President Biden has now stated that he will lift all restrictions relating to the COVID-19 (and the declaration of a Public Health Emergency) on May 11, 2022, there are backlogs of filings and other issues that may arise that delay the United States review of applications. For example, there may be a prolonged government shutdown, or if other global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Even if we obtain FDA approval of any of our product candidates, we may never obtain approval or commercialize such products outside of the United States, which would limit our ability to realize their full market potential.

In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not mean that regulatory approval will be obtained in any other countries. Approval procedures vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking regulatory approvals in various jurisdictions could result in significant delays, difficulties and costs for us and may require additional preclinical studies or clinical trials which would be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. Satisfying these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. In addition, our failure to obtain regulatory approval in any country may delay or have negative effects on the process for regulatory approval in other countries. We do not have any product candidates approved for sale in any jurisdiction, including international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, our ability to realize the full market potential of our products will be harmed.

We are conducting clinical trials and may in the future conduct additional clinical trials for our product candidates outside the United States and/or China, and FDA, NMPA and similar foreign regulatory authorities may not accept data from such trials.

We are conducting clinical trials and may in the future conduct additional clinical trials for our product candidates outside the United States, including in Australia, Europe or other foreign jurisdictions. The acceptance of trial data from clinical trials conducted outside the United States by the FDA may be subject to certain conditions. In cases where data from clinical trials conducted outside the United States are intended to serve as the sole basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the United States population and United States medical practice; (ii) the trials were performed by clinical investigators of recognized competence and (iii) the data may be considered valid without the need for an on-site inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. Otherwise, for studies that are conducted at sites outside of the United States and not subject to an IND and which are intended to support a marketing application (but which are not intended to serve as the sole basis for marketing approval), the FDA requires the clinical trial to have been conducted in accordance with good clinical practice, or GCP, requirements and the FDA must be able to validate the data from the clinical trial through an on site inspection if it deems such inspection necessary. Additionally, the FDA's clinical trial requirements, including sufficient size of patient populations, statistical powering, and specific documentation requirements must be met. Many foreign regulatory bodies, such as NMPA, have similar approval requirements. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. There can be no assurance that the FDA, NMPA or any similar foreign regulatory authority will accept data from trials conducted outside of the United States or the applicable jurisdiction. If the FDA, NMPA or any similar foreign regulatory authority does not accept such data, it would result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan, and which may result in our product candidates not receiving approval or clearance for commercialization in the applicable jurisdiction.

Our product candidates may cause undesirable adverse events, side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following any regulatory approval.

Undesirable adverse events caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA, NMPA or other comparable regulatory authority. Results of our trials could reveal a high and unacceptable severity or prevalence of adverse events. In such an event, our trials could be suspended or terminated and the FDA, NMPA or other comparable regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Drug-related adverse events could affect patient recruitment or the ability of enrolled subjects to complete the trial, and could result in potential product liability claims. Moreover, such events may require us to amend our trials, including reducing the dosage in our clinical trials.

For instance, in September 2019, the FDA placed a clinical hold on our Phase 1 trial of ADG116 (ADG116-1001) in the United States after we reported to the FDA the death of the only patient dosed in the trial. We revised the study protocol to mitigate the risk of drug-induced liver toxicity, lower the starting dose of ADG116, and tighten the inclusion and exclusion criteria. The FDA removed the clinical hold on this protocol on December 5, 2019. In parallel, we initiated a new Phase 1 clinical trial of ADG116 (ADG116-1003) in Australia and completed multiple levels of dose escalation without serious adverse events. In March 2021, we submitted this new protocol for ADG116 (ADG116-1003) to FDA with safety data from Australia. Upon receiving clearance from FDA to open sites in the United States for ADG116-1003, we terminated the prior Phase 1 trial (ADG116-1001) in the United States for business reasons. Overall, we have evaluated ADG116 monotherapy in approximately 50 patients up to 10 mg/kg with repeat dosing and the majority of reported TRAEs were Grade 1/2 (56%), with one DLT event (Grade 4 hyperglycemia) at the 10 mg/kg dose level.

We cannot provide any assurance that there will not be treatment-related severe adverse events with our product candidates, that the trials for our product candidates will not be suspended in the future, or that patient recruitment for trials with our product candidates will not be adversely impacted by the ADG116 related adverse events, any of which could materially and adversely affect our business and prospects. Further, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients and limited duration of exposure, rare and severe side effects of our product candidates may only be uncovered with a significantly larger number of patients exposed to the product candidate. In the event that any of our product candidates receives marketing approval and we or others later identify undesirable or unacceptable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- we may suspend marketing of such products;
- regulatory authorities may withdraw or limit approvals of such products or require us to take an approved product off the market;
- regulatory authorities may require the addition of labeling statements, specific warnings, a contraindication or field alerts to physicians and pharmacies, or issue other communications containing warnings or other safety information about the product;
- regulatory authorities may require a medication guide outlining the risks of such side effects for distribution to patients, or that we implement a REMS plan to ensure that the benefits of the product outweigh its risks or to develop a similar strategy as required by a comparable regulatory authority, that may, for instance, restrict distribution of our drugs and impose burdensome implementation requirements on us;
- we may be required to conduct post-market studies;
- we may be subject to limitations on how we may promote or manufacture the product;
- sales of the product may decrease significantly;
- we could be sued and held liable for harm caused to subjects or patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

Further, combination therapy involves unique adverse events that could be exacerbated compared to adverse events from monotherapies. These types of adverse events could be caused by our product candidates and could also cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA, NMPA or other comparable regulatory authority. Results of our trials could reveal a high and unacceptable severity or prevalence of adverse events.

We may seek Orphan Drug Designation for some of our product candidates, and we may be unsuccessful.

Regulatory authorities in some jurisdictions, including the United States, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a drug as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a disease with a patient population of fewer than 200,000 individuals in the United States, or a patient population of greater than 200,000 individuals in the United States, but for which there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States.

Generally, if a drug with an Orphan Drug Designation subsequently receives the first FDA approval for the disease for which it has such designation, the drug is entitled to a period of marketing exclusivity, which precludes the FDA from approving another marketing application for the same drug for the same indication during the period of exclusivity. The applicable period is seven years in the United States. Orphan Drug exclusivity may be lost if the FDA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

Even if we obtain Orphan Drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition and the same drugs can be approved for a different condition but used off-label for any orphan indication we may obtain. Even after an orphan drug is approved, the FDA may subsequently approve a different drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

We may attempt to secure approval from the FDA or comparable foreign regulatory authorities through the use of accelerated approval pathways. If we are unable to obtain such approval, we may be required to conduct additional preclinical studies or clinical trials beyond those that we contemplate, which could increase the expense of obtaining, and delay the receipt of, necessary marketing approvals. Even if we receive accelerated approval from the FDA, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post-marketing requirements, the FDA may seek to withdraw accelerated approval.

We may in the future seek an accelerated approval for our one or more of our product candidates. Under the accelerated approval program, the FDA may grant accelerated approval to a product candidate designed to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the product candidate has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is usually contingent on the sponsor’s agreement to conduct, in a diligent manner, additional post- approval confirmatory studies to verity and describe the drug’s clinical benefit. If such post-approval studies fail to confirm the drug’s clinical benefit, the FDA may withdraw its approval of the drug.

Prior to seeking accelerated approval for any of our product candidates, we intend to obtain a meeting and meet with the FDA and will otherwise evaluate our ability to seek and receive accelerated approval. There can be no assurance that after our evaluation of the feedback and other factors we will decide to pursue or submit a BLA for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that after subsequent FDA feedback we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, if we decide to submit an application for accelerated approval or receive an expedited regulatory designation (e.g., breakthrough therapy designation) for our product candidates, there can be no assurance that such submission or application will be accepted or that any expedited development, review or approval will be granted on a timely basis, or at all. The FDA or other comparable foreign regulatory authorities could also require us to conduct further studies prior to considering our application or granting approval of any type. A failure to obtain accelerated approval or any other form of expedited development, review or approval for our product candidate would result in a longer time period to commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

Even if we receive regulatory approvals for our product candidates, we will be subject to ongoing regulatory obligations and continued regulatory reviews, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our product candidates.

If our product candidates are approved, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, import, export, adverse event reporting, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable regulatory authorities.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, NMPA and comparable regulatory authority requirements, including, in the United States, ensuring that quality control and manufacturing procedures conform to current cGMP regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any BLA, other marketing application, and previous responses to inspection observations. Accordingly, we and others with whom we work must continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the drug may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase IV clinical trials and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a REMS program as a condition of approval of our product candidates, which could entail requirements for long-term patient follow-up, a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA, NMPA, or a comparable regulatory authority approves our product candidates, we will have to comply with requirements including, for example, submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs and Good Clinical Practices, or cGCPs, for any clinical trials that we conduct post approval.

The FDA and NMPA may impose consent decrees or withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the drug reaches the market. Later discovery of previously unknown problems with our product candidates, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information, imposition of post-market studies or clinical trials to assess new safety risks, or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of our drugs, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- fines, untitled or warning letters, or holds on clinical trials;
- refusal by the FDA, NMPA or comparable regulatory authorities to approve pending applications or supplements to approved applications filed by us or suspension or revocation of license approvals;
- product seizure or detention, or refusal to permit the import or export of our product candidates; and
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA, NMPA and other regulatory authorities actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. The policies of the FDA, NMPA and of other regulatory authorities may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any regulatory approval that we may have obtained and we may not achieve or sustain profitability.

All material aspects of the research, development and commercialization of pharmaceutical products are heavily regulated.

All jurisdictions in which we intend to conduct our pharmaceutical-industry activities regulate these activities in great depth and detail. We intend to focus our activities in the major markets such as the United States and China. These jurisdictions strictly regulate the pharmaceutical industry, and in doing so they employ broadly similar regulatory strategies, including regulation of product development and approval, manufacturing, and marketing, sales and distribution of products. However, there are differences in the regulatory regimes that make for a more complex and costly regulatory compliance burden for a company like ours that plans to operate in these regions.

The process of obtaining regulatory approvals and compliance with appropriate laws and regulations require substantial time and financial resources. Failure to comply with the applicable requirements at any time during the product development process and approval process, or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include: refusal to approve pending applications; withdrawal of an approval; license revocation; clinical hold; voluntary or mandatory product recalls; product seizures; total or partial suspension of production or distribution; injunctions; fines; refusals of government contracts; providing restitution; undergoing disgorgement; or other civil or criminal penalties. Failure to comply with these regulations could have a material adverse effect on our business.

Future strategic partnerships may be important to us. We will face significant competition in seeking new strategic partners.

We do not yet have any capability for manufacturing, sales, marketing or distribution. For some of our product candidates, we may in the future determine to collaborate with pharmaceutical and biotechnology companies for development and potential commercialization of therapeutic products. The competition for strategic partners is intense. Our ability to reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the strategic partner's resources and expertise, the terms and conditions of the proposed collaboration and the proposed strategic partner's evaluation of a number of factors. These factors may include the design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The strategic partner may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such collaboration could be more attractive than the one with us for our product candidate.

Strategic partnerships are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future strategic partners. Even if we are successful in entering into collaboration, the terms and conditions of that collaboration may restrict us from entering into future agreements with other potential collaborators.

If we are unable to reach agreements with suitable strategic partners on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into strategic partnerships and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our technology platform and our business may be materially and adversely affected. Any collaboration may be on terms that are not optimal for us, and we may not be able to maintain any new collaboration if, for example, development or approval of a product candidate is delayed, sales of an approved product candidate do not meet expectations or the partner terminates the collaboration. Any such collaboration, or other strategic transaction, may require us to incur non-recurring or other charges, and increase our near- and long-term expenditures and pose significant integration or implementation challenges or disrupt our management or business. Accordingly, although there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete may be subject to the foregoing or other risks and have a material and adverse effect on our business, financial condition, results of operations, and prospects. Conversely, any failure to enter any collaboration or other strategic transaction that would be beneficial to us could delay the development and potential commercialization of our product candidates and have a negative impact on the competitiveness of any product candidate that reaches the market.

We may not be able to enter into additional collaboration agreements beyond our existing clinical trial collaboration with Roche, technology licensing agreements with Sanofi, Exelixis and ADC Therapeutics, our outlicensing agreements with Guilin Sanjin and Dragon Boat, or Discovery Agreements such as those with NIH, Tanabe, Celgene, GSK, Hengrui and others. If we are unable to maintain existing and future strategic partnerships or collaborations, or if these strategic partnerships or collaborations are not successful, our business could be adversely affected.

Our existing strategic partnerships, collaborations and any future strategic partnerships we enter into may pose a number of risks, including the following:

- we may not be able to enter into critical strategic partnerships or enter into them on favorable terms;
- strategic partners or collaborators have significant discretion in determining the effort and resources that they will apply to such a partnership, and they may not perform their obligations as agreed, expected, or in compliance with applicable legal requirements;
- strategic partners or collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the partners' strategic focus or available funding, or external factors, such as an acquisition that diverts resources or creates competing priorities;
- strategic partners or collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- strategic partners or collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the strategic partners or collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than our product candidates;
- product candidates discovered in collaboration with us may be viewed by our strategic partners or collaborators as competitive with their own product candidates or products, which may cause strategic partners or collaborators to cease to devote resources to the commercialization of our product candidates;

- a strategic partner or collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product candidates;

- disagreements with strategic partners or collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

- strategic partners or collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

- strategic partners or collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;

- strategic partners or collaborators may claim for a substantial compensation for our failure of development of the product candidates specified under the relevant out-licensing agreements that solely arose out of problems of our previous R&D basis; and

- strategic partnerships or collaborations may be terminated for the convenience of the partner or the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If any partnerships or collaboration we enter into do not result in the successful development of our product candidates or if one of our partners or collaborator terminates the agreement with us, our continued development of our product candidates could be delayed and our business may be materially and adversely affected.

We will need to grow our organization, and we may experience difficulties in managing this growth, which could disrupt our operations.

As of December 31, 2022, we had 248 full-time employees. As our development and commercialization plans and strategies develop, we expect to expand our employee base for managerial, operational, financial and other resources. As our product candidates enter and advance through preclinical studies and clinical trials, we will need to expand our development, regulatory and manufacturing capabilities or contract with other organizations to provide these capabilities for us. In the future, we expect to enter into additional relationships with collaborators or partners, suppliers and other organizations and establish a sales and marketing team in preparation for commercialization activities. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls. Our inability to successfully manage our growth and expand our operations could have a material and adverse effect on our business, financial condition, results of operations and prospects.

Disruptions in the financial markets and economic conditions could affect our ability to raise capital.

Global economies could suffer dramatic downturns as the result of a deterioration in the credit markets and related financial crisis as well as a variety of other factors including, extreme volatility in security prices, severely diminished liquidity and credit availability, ratings downgrades of certain investments and declining valuations of others. In the past, governments have taken unprecedented actions in an attempt to address and rectify these extreme market and economic conditions by providing liquidity and stability to the financial markets. If these actions are not successful, the return of adverse economic conditions may cause a significant impact on our ability to raise capital, if needed, on a timely basis and on acceptable terms or at all.

In addition, there is considerable uncertainty over the long-term effects of the expansionary monetary and fiscal policies adopted by the central banks and financial authorities of some of the world's leading economies, including the United States and China. There have been concerns over unrest and terrorist threats in the Middle East, Europe and Africa and over the conflicts involving Ukraine, Syria and North Korea. There have also been concerns on the relationship among China and other Asian countries, which may result in or intensify potential conflicts in relation to territorial disputes or the trade related disputes between the United States and China. In addition, the U.K. held a referendum on June 23, 2016 on its membership in the EU, in which voters approved an exit from the EU, commonly referred to as "Brexit''; the U.K. formally left the EU on January 31, 2020. The EU and the U.K have entered into the post-Brexit Trade and Cooperation Agreement, an agreement purporting to create a broad economic partnership between the EU and the U.K., which was approved by the European Parliament in April 2021 and went into force fully on May 1, 2021. Nonetheless, Brexit could still adversely affect European and worldwide economic and market conditions and could contribute to instability in global financial and foreign exchange markets. It is unclear whether these challenges and uncertainties will be contained or resolved, and what effects they may have on the global political and economic conditions in the long term.

If we face allegations of non-compliance with laws and encounter sanctions, our reputation, revenues and liquidity may suffer, and our product candidates and approved products, if any, could be subject to restrictions or withdrawal from the market.

Any government investigation of alleged violations of laws or regulations could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to obtain approvals commercialize and generate revenues from our drugs. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected. Additionally, if we are unable to generate revenues from our product sales, our potential for achieving profitability will be diminished and the capital necessary to fund our operations will be increased.

Our reputation is important to our success. Negative publicity may adversely affect our reputation and business prospects.

Any negative publicity concerning us, our affiliates or any entity that shares the "Adagene'' name, even if untrue, could adversely affect our reputation and business prospects. There can be no assurance that negative publicity about us or any of our affiliates or any entity that shares the "Adagene'' name would not damage our brand image or have a material adverse effect on our business, results of operations and financial condition.

Potential future acquisitions or strategic collaborations may increase our capital requirements, dilute our shareholders, cause us to incur debt or assume contingent liabilities and subject us to other risks.

We may evaluate various acquisitions and strategic collaborations, including licensing or acquiring complementary products, intellectual property rights, technologies or businesses. Any potential acquisition or strategic collaboration may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent liabilities;
- assimilation of operations, intellectual property and products of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing product programs and initiatives in pursuing such a strategic merger or acquisition;
- retention of key employees, the loss of key personnel, and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products or product candidates and regulatory approvals; and/or

- our inability to generate revenue from acquired technology and/or products sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

In addition, if we undertake acquisitions, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense. Moreover, we may not be able to locate suitable acquisition opportunities and this inability could impair our ability to grow or obtain access to technology or products that may be important to the development of our business.

Our business operations and current or future relationships with healthcare professionals, principal investigators, consultants, customers and third-party payors in the United States and elsewhere may be subject, directly or indirectly, to applicable anti-kickback, fraud and abuse, false claims, physician payment transparency and other healthcare laws and regulations. If we or our employees, independent contractors, consultants, commercial partners, or vendors violate these laws, we could face substantial penalties.

Our business operations and current or future arrangements with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute our product candidates, if approved. Such laws include, without limitation:

- the U.S. federal civil and criminal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or providing any remuneration (including any kickback, bribe, or certain rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under U.S. federal and state healthcare programs such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the U.S. federal false claims laws, including the False Claims Act, which can be enforced through whistleblower actions, and civil monetary penalties laws, which, among other things, impose criminal and civil penalties against individuals or entities for knowingly presenting, or causing to be presented, to the U.S. federal government, claims for payment or approval that are false or fraudulent, knowingly making, using or causing to be made or used, a false record or statement material to a false or fraudulent claim, or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services; similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;

- the United States Physician Payments Sunshine Act and its implementing regulations, which require certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid or the Children’s Health Insurance Program to report annually to the government information related to certain payments and other transfers of value to physicians, as defined by such law, and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective January 1, 2022, the U.S. federal physician transparency reporting requirements will extend to include transfers of value made during the previous year to certain non-physician providers such as physician assistants and nurse practitioners;

- analogous U.S. state laws and regulations, including: state anti-kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales;

- the U.S. Foreign Corrupt Practices Act of 1977, as amended, which prohibits, among other things, U.S. companies and their employees and agents from authorizing, promising, offering or providing, directly or indirectly, corrupt or improper payments or anything else of value to foreign government officials, employees of public international organizations and foreign government owned or affiliated entities, candidates for foreign political office and foreign political parties or officials thereof; and

- marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payor, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state and local laws that require the registration of pharmaceutical sales representatives; and state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities. For detailed discussion on material applicable PRC regulation, see "Item 4 Information on the Company—PRC Regulation" Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from government-funded healthcare programs, such as Medicare and Medicaid or similar programs in other countries or jurisdictions, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations. Further, defending against any such actions can be costly and time-consuming and may require significant personnel resources. Even if we are successful in defending against any such actions that may be brought against us, our business may be impaired.

Recently enacted and future legislation in the United States and other countries may affect the prices we may obtain for our product candidates and increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates.

In the United States and many other countries, rising healthcare costs have been a concern for governments, patients and the health insurance sector, which resulted a number of changes to laws and regulations, and may result in further legislative and regulatory action regarding the healthcare and health insurance systems that could affect our ability to profitably sell any product candidates for which we obtain marketing approval.

For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the ACA, was enacted in the United States in March 2010 with the stated goals of containing healthcare costs, improving quality and expanding access to healthcare, and includes measures to change health care delivery, increase the number of individuals with insurance, ensure access to certain basic health care services, and contain the rising cost of care. Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, various portions of the ACA are currently facing legal and constitutional challenges in the Fifth Circuit Court of Appeals and the United States Supreme Court. Additionally, the current administration has issued various Executive Orders which eliminated cost sharing subsidies and various provisions that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices, and Congress has introduced several pieces of legislation aimed at significantly revising or repealing the ACA. It is unclear whether the ACA will be overturned, repealed, replaced, or further amended.

In addition, other federal health reform measures have been proposed and adopted in the United States. For example, as a result of the Budget Control Act of 2011, providers are subject to Medicare payment reductions of 2% per fiscal year through 2030, with the exception of a temporary suspension from May 1, 2020 through December 31, 2020, unless additional Congressional action is taken. Further, the American Taxpayer Relief Act of 2012 reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments from providers from three to five years. The Medicare Access and CHIP Reauthorization Act of 2015 also introduced a quality payment program under which certain individual Medicare providers will be subject to certain incentives or penalties based on new program quality standards. Payment adjustments for the Medicare quality payment program began in 2019. At this time, it is unclear how the introduction of the quality payment program will impact overall physician reimbursement under the Medicare program. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

Further, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics.

Since January 2017, there has been legislation considered in Congress to restrict the pricing of drug products to a governmental negotiated rate or to other similar rates that would reduce the costs to government, commercial payers and individuals. In July 2020, President Trump signed four Executive Orders directing the Department of Health and Human Services and other agencies to take specific actions to reduce prescription drug prices. The first order directs federally qualified health centers to pass along significant discounts on insulin and epinephrine from drug companies to low-income individuals. The second order would allow the important of prescription drugs from Canada into the United States where the prices are deemed to be lower. The third order would eliminate safe harbor protections under the federal Anti-Kickback Statute that currently covers rebates paid by manufacturers to Medicare Part D plans and Medicaid managed care organizations, either directly or through pharmacy benefit managers under contract with such plans or organizations, so long as such actions are not projected to increase federal spending, Medicare beneficiary premiums or patients' total out-of-pocket cases. The fourth order will reduce the payment for Medicare part B drugs to be paid at the same rate as other developed nations, thereby reducing the reimbursement. All of these Executive Orders require rulemaking prior to implementation and could be stalled by Congress or the next election.

The combination of healthcare cost containment measures, increased health insurance costs, reduction of the number of people with health insurance coverage, as well as future legislation and regulations focused on reducing healthcare costs by reducing the cost of or reimbursement and access to pharmaceutical products, may limit or delay our ability to generate revenue, attain profitability, or commercialize our pipeline products, if approved.

We face intense competitions and rapid technological changes, as well as the possibility that our competitors may develop therapies that are similar, more advanced, or more effective than ours, which may adversely affect our ability to successfully commercialize our product candidates and our financial condition.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We are currently aware of various existing therapies and development candidates that may compete with our wholly owned clinical candidates as they engage similar targets, such as agents targeting CD137 and CTLA-4, and bispecifics targeting both. We have competitors in the United States, China and internationally, including major multinational pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies. Many of our competitors have substantially greater financial, technical, and other resources, such as larger research and development, marketing and manufacturing organizations. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. As a result, these companies may obtain regulatory approval more rapidly than we are able to and may be more effective in selling and marketing their products as well. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, products that are more effective or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization and market penetration than we do. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

We have no experience in launching and marketing product candidates. We may not be able to effectively build and manage our sales network, or benefit from third-party collaborators' sales network.

We currently have no manufacturing, sales, marketing or commercial product distribution capabilities and have no experience in marketing drugs. We intend to develop an in-house marketing organization and sales force, which will require significant capital expenditures, management resources and time. We will have to compete with other biopharmaceutical companies to recruit, hire, train and retain marketing and sales personnel.

Given that marketing generally requires extensive training and oversight, and if we are unable or decide not to establish internal sales, marketing and commercial distribution capabilities for any or all of the drugs we develop, we will likely pursue collaborative arrangements regarding the sales and marketing of our product candidates, if approved. However, there can be no assurance that we will be able to establish or maintain such collaborative arrangements, or, if we are able to do so, that they will have effective sales forces. Any revenue we receive will depend on the efforts of such third parties, which may not be successful. We may have little or no control over the marketing and sales efforts of such third parties, and our revenue from product sales may be lower than if we had commercialized our product candidates ourselves. We will also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates, if approved.

There can be no assurance that we will be able to develop in-house sales, marketing and commercial distribution capabilities or establish or maintain relationships with third-party collaborators to successfully commercialize any product candidate, if approved, and as a result, we may not be able to generate product sales revenue.

Even if we are able to commercialize any approved product candidates, coverage and reimbursement may be limited or unavailable in certain market segments for our product candidates, and we may be subject to unfavorable pricing regulations, which could harm our business.

The regulations that govern regulatory approvals, pricing and reimbursement for new therapeutic products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or licensing approval is granted. In some non-U.S. markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain regulatory approval for a drug in a particular country, but then be subject to price regulations that delay our commercial launch of the drug and negatively impact our revenues.

A primary trend in the global healthcare industry is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Our ability to commercialize any drugs successfully also will depend in part on the extent to which coverage and reimbursement for these drugs and related treatments will be available on adequate terms, or at all, from government health administration authorities, private health insurers and other organizations.

In the United States, no uniform policy of coverage and reimbursement for biopharmaceutical products exists among third-party payors. As a result, obtaining coverage and reimbursement approval of a drug from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our drugs on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. Even if we obtain coverage for a given drug, the resulting reimbursement rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Increasingly, third-party payors are requiring that companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Additionally, third-party payors may not cover, or provide adequate reimbursement for, long-term follow-up evaluations required following the use of our genetically modified drugs. Patients are unlikely to use our drugs and any approved product candidates unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of the drug. Because some of our product candidates have a higher cost of goods than conventional therapies, may require long-term follow up evaluations, and will likely be administered under the supervision of a physician, the risk that coverage and reimbursement rates may be inadequate for us to achieve profitability may be greater.

If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate that we successfully develop.

There may be significant delays in obtaining reimbursement for approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or other comparable regulatory authorities outside the United States. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Payment rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on payments allowed for lower cost drugs that are already reimbursed, and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future weakening of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for our drugs and any new product candidates that we develop could have a material adverse effect on our business, our operating results, and our overall financial condition.

In China, the Ministry of Human Resources and Social Security of China or provincial or local human resources and social security authorities, together with other government authorities, review the inclusion or removal of drugs from China's National Drug Catalog for Basic Medical Insurance, Work-related Injury Insurance and Maternity Insurance, or the National Reimbursement Drug List, or the NRDL, or provincial or local medical insurance catalogues for the National Medical Insurance Program regularly, and the tier under which a drug will be classified, both of which affect the amounts reimbursable to program participants for their purchases of those drugs. There can be no assurance that our drugs and any approved product candidates will be included in the NRDL or provincial reimbursements lists. Products included in the NRDL have been typically generic and essential drugs. Innovative drugs similar to our product candidates have historically been more limited on their inclusion in the NRDL due to the affordability of the government's Basic Medical Insurance, although this has been changing in recent years. According to currently effective PRC laws and regulations, the prices of approved drugs are determined by market competition. The government regulate prices mainly by establishing a consolidated procurement mechanism, revising the NRDL and strengthening regulation of medical and pricing practices. We cannot predict the extent to which our business may be affected by potential future legislative or regulatory developments. Changes in pricing regulation could restrict the amount that we are able to charge for our future approved drugs, which would adversely affect our revenue, profitability and results of operations.

We intend to seek approval to market our product candidates in the United States, China and in other jurisdictions. In some non-U.S. countries, the pricing of drugs and biologics is subject to governmental control, which can take considerable time even after obtaining regulatory approval. Market acceptance and sales of our drugs will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for drugs and may be affected by existing and future health care reform measures.

As we engage in collaboration worldwide, we may be exposed to specific risks of conducting our business and operations in international markets.

We are a biotechnology company with global footprints. We are currently building our clinical and technology infrastructures to support our future global operations and prepare to serve global markets. If we fail to obtain applicable licenses or fail to enter into strategic collaboration arrangements with third parties in these markets, or if these collaboration arrangements turn out unsuccessful, our revenue-generating growth potential will be adversely affected.

Moreover, international business relationships subject us to additional risks that may materially adversely affect our ability to attain or sustain profitable operations, including:

- efforts to enter into collaboration or licensing arrangements with third parties in connection with our international sales, marketing and distribution efforts may increase our expenses or divert our management's attention from the acquisition or development of product candidates;
- changes in a specific country's or region's political and cultural climate or economic condition;
- differing regulatory requirements for drug approvals and marketing internationally;
- difficulty of effective enforcement of contractual provisions in local jurisdictions;

- potentially reduced protection for intellectual property rights;
- potential third-party patent rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation or political instability;
- compliance with tax, employment, immigration and labor laws for employees traveling abroad;
- the effects of applicable tax structures and potentially adverse tax consequences;
- currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incidental to doing business in another country;
- workforce uncertainty and labor unrest and failure to comply with the applicable laws and regulations in relation to management of the employment of foreigners within the PRC;
- the potential for so-called parallel importing, which is what happens when a local seller, faced with high or higher local prices, opts to import goods from an international market with low or lower prices rather than buying them locally;
- failure of our employees and contracted third parties to comply with Office of Foreign Assets Control rules and regulations and the Foreign Corrupt Practices Act of the United States, and other applicable rules and regulations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters, including earthquakes, volcanoes, typhoons, floods, hurricanes and fires.

These and other risks may materially adversely affect our ability to attain or sustain revenue from international markets.

Building our commercialization capabilities will require significant investment of time and money. There would be no assurance that we will successfully set up our commercialization capabilities in any of the proposed jurisdictions or at all, or that we will successfully commercialize any of our product candidates in the future.

We are currently in the early stages of building and expanding our commercial capabilities to allow us to market our own products, if approved, in the future. We will need to set up full commercialization capabilities in the jurisdictions, including China and the United States, which would require substantial investment of time and money and will divert significant management focus and resources. We also face competition with multinational and local pharmaceutical and biotechnology companies with established commercialization capabilities in terms of marketing and attracting talents.

Therefore, there can be no assurance that our efforts to set up commercialization capabilities will be successful in any of the proposed jurisdictions or at all.

Even if ADG116, ADG126, ADG106, ADG206 or one of our other proprietary product candidates obtains regulatory approval, we may determine that commercializing such product candidate ourselves would not be the most effective way to create value for our shareholders or holders of ADSs. In addition, if we choose to commercialize any of our product candidates, our marketing efforts may be unsuccessful as a result of unfavorable pricing or reimbursement limitations, delays, competition or other factors. Failure to successfully market one or more of our approved products, or delays in our commercialization efforts, may diminish the commercial prospects for such products and may result in financial losses or damage to our reputation, each of which may have a negative impact on the market price of our ADSs and our financial condition, results of operations and future growth prospects.

We may continue to pursue collaborations or licensing arrangements, joint ventures, strategic alliances, partnerships or other strategic investment or arrangements, which may fail to produce anticipated benefits and adversely affect our operations.

We may continue to pursue opportunities for collaboration, out-license, joint ventures, acquisitions of products, assets or technology, strategic alliances, or partnerships that we believe would advance our development. We may consider pursuing growth through the acquisition of technology, assets or other businesses that may enable us to enhance our technologies and capabilities. Proposing, negotiating and implementing these opportunities may be a lengthy and complex process. Other companies, including those with substantially greater financial, marketing, technology, or other business resources, may compete with us for these opportunities or arrangements. We may not be able to identify, secure, or complete any such transactions or arrangements in a timely manner, on a cost-effective basis, on acceptable terms, or at all.

We have limited experience with respect to these business development activities. Management and integration of a licensing arrangement, collaboration, joint venture or other strategic arrangement may disrupt our current operations, decrease our profitability, result in significant expenses, or divert management resources that otherwise would be available for our existing business. We may not realize the anticipated benefits of any such transaction or arrangement.

Furthermore, partners, collaborators, or other parties to such transactions or arrangements may fail to fully perform their obligations or meet our expectations or cooperate with us satisfactorily for various reasons and subject us to potential risks, including the followings:

- partners, collaborators, or other parties have significant discretion in determining the efforts and resources that they will apply to a transaction or arrangement;
- partners, collaborators, or other parties could independently develop, or develop with third parties, services and products that compete directly or indirectly with our product candidates;
- partners, collaborators, or other parties may stop, delay or discontinue clinical trials as well as repeat clinical trials or conduct new clinical trials by using our intellectual property or proprietary information;
- partners, collaborators, or other parties may not properly maintain or defend our intellectual property rights or may use our intellectual property or proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential liabilities;
- disputes may arise between us and partners, collaborators, or other parties that cause the delay or termination of the research, development or commercialization of our product candidates, or that result in costly litigation or arbitration that diverts management’s attention and resources;
- partners, collaborators, or other parties may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable services and products; and
- partners, collaborators, or other parties may own or co-own intellectual properties covering our product candidates that results from our collaborating with them, and in such cases, we would not have the exclusive right to commercialize such intellectual properties.

Any such transactions or arrangements may also require actions, consents, approval, waiver, participation or involvement of various degrees from third parties, such as regulators, government authorities, creditors, licensors or licensees, related individuals, suppliers, distributors, shareholders or other stakeholders or interested parties. There is no assurance that such third parties will be cooperative as we desire, or at all, in which case we may be unable to carry out the relevant transactions or arrangements.

We rely on third parties to support, conduct and monitor our preclinical studies and clinical trials. Therefore, we may not be able to directly control the timing, process, expense and quality of our clinical trials and we cannot assure these third parties can duly perform their obligations as agreed and expected.

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators and third-party CROs, to conduct our preclinical studies and clinical trials and to monitor and manage data for our ongoing preclinical and clinical programs. We rely on these parties for execution of our preclinical studies and clinical trials, and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our studies and trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities for all of our products candidates in clinical development. Regulatory authorities enforce these GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat or suspend clinical trials, which would delay the regulatory approval process.

Further, these investigators and CROs are not our employees and we will not be able to control, other than by contract, the amount of resources, including time, which they devote to our product candidates and clinical trials. If independent investigators or CROs fail to devote sufficient resources to the development of our product candidates, or if their performance is substandard, it may delay or compromise the prospects for approval and commercialization of any product candidates that we develop. In addition, the use of third-party service providers may require us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated.

Our CROs have the right to terminate their agreements with us in the event of an uncured material breach. In addition, some of our CROs have an ability to terminate their respective agreements with us if it can be reasonably demonstrated that the safety of the subjects participating in our clinical trials warrants such termination, if we make a general assignment for the benefit of our creditors or if we are liquidated.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Additionally, CROs may lack the capacity to absorb higher workloads or take on additional capacity to support our needs. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

We currently rely on a third-party manufacturer to produce our product candidates. Any failure by the third-party manufacturer to produce acceptable product candidates for us pursuant to our specifications and regulatory standards may delay or impair our ability to initiate or complete our clinical trials, obtain and maintain regulatory approvals or commercialize approved products, if any.

We currently rely on a third-party manufacturer and expect to continue to rely for some time on third parties to manufacture our product candidates for preclinical testing and clinical trials, in compliance with applicable regulatory and quality standards, and may do so for the commercial manufacture of some of our product candidates, if approved. To date, we have obtained bulk drug substance for ADG116, ADG126, ADG106 and ADG206 from a single-source third-party contract manufacturer. Any reduction or halt in supply of the drug substance from such contract manufacturer could severely constrain our ability to develop our product candidates until a replacement contract manufacturer is found and qualified. If we are unable to arrange for and maintain such third-party manufacturing sources that are capable of meeting regulatory standards, or fail to do so on commercially reasonable terms, we may not be able to successfully produce sufficient supply of product candidate or we may be delayed in doing so. If we were to experience an unexpected loss of supply of our product candidates, for any reason, whether as a result of manufacturing, supply or storage issues or otherwise, we could experience delays, disruptions, suspensions or terminations of, or be required to restart or repeat, any pending or ongoing clinical trials. Such failure or substantial delay or loss of supply could materially harm our business. We are continuously evaluating multiple vendors both in China and abroad to ensure that we have a continuous supply of products for global trials.

We may have little to no control regarding the occurrence of third-party manufacturer incidents. Any failure by our third-party manufacturer to comply with good manufacturing practices, or GMPs, or failure to scale up manufacturing processes, including any failure to deliver sufficient quantities of product candidates in a timely manner, would lead to a delay in, or failure to seek or obtain, regulatory approval of any of our product candidates. Furthermore, any change in manufacturer of our product candidates or approved products, if any, would require new regulatory approvals, which could delay completion of clinical trials or disrupt commercial supply of approved products.

Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to commercialize any product candidates that receive marketing approval on a timely and competitive basis.

In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer, we may have difficulty transferring such skills or technology to another third party and a feasible alternative many not exist. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our product candidates. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget.

If our current research collaborators or scientific advisors and employees terminate their relationships with us or develop relationships with our competitors, our ability to discover antibodies and to conduct research and development could be adversely affected.

The responsibility of overseeing research and development of our product candidates is concentrated among a number of key research collaborators and/or scientific advisors. There can be no assurance that there will not be a detrimental impact on us if one or more of these key research collaborators and/or scientific advisors were to cease relationship or employment with us, potentially as a result of lateral recruitment by existing or new competitors. As a result, this may adversely affect our ability to conduct research and development on antibody product candidates.

Furthermore, our ability to continue to conduct and expand operations depends on our ability to attract and retain a large and growing number of personnel. The ability to meet our expertise needs, including the ability to find qualified personnel to fill positions that become vacant at our research and development department or to collaborate with us in research and development efforts, while controlling our costs, is generally subject to numerous external factors, including the availability of a sufficient number of qualified persons in the biopharmaceutical industry, the unemployment levels within those markets, prevailing wage rates, changing demographics, health and other insurance costs and adoption of new or revised employment and labor laws and regulations. If we are unable to locate, to attract or to retain qualified personnel, the quality of services and products provided to customers may decrease and our financial performance may be adversely affected. In addition, if costs of labor or related costs to maintain relationships with research collaborators increase for other reasons or if new or revised labor laws, rules or regulations or healthcare laws are adopted or implemented that further increase labor costs, our business, financial condition and results of operations could be materially adversely affected.

We may not be able to attract and retain key senior management members or research and development personnel.

Our future success depends upon the continuing services of members of our senior management team and key research and development personnel and consultants. Although we typically require our key personnel to enter into non-compete and confidentiality agreements with us, we cannot prevent them from joining our competitors after the non-compete period. The loss of their services could adversely impact our ability to achieve our business objectives. If one or more of our senior management or key clinical and scientific personnel are unable or unwilling to continue in their present positions or joins a competitor or forms a competing company, we may not be able to replace them in a timely manner or at all, which will have a material and adverse effect on our business, financial condition and results of operations. We do not maintain "key person" insurance for any of our executives or other employees.

In addition, the continued growth of our business depends on our ability to hire additional qualified personnel with expertise in molecular biology, chemistry, biological information processing, computational biology, software, engineering, sales, marketing, and technical support. We compete for qualified management and scientific personnel with other life science and technology companies, universities, and research institutions in China and overseas. Competition for these individuals is intense, and the turnover rate can be high. Failure to attract and retain management and scientific and engineering personnel could prevent us from pursuing collaborations or developing our product candidates or technologies.

We face risks related to health epidemics, severe weather conditions and other outbreaks.

China has in the past experienced significant natural disasters, including earthquakes, extreme weather conditions, as well as health scares related to epidemic diseases, and any similar event could materially impact our business in the future. If a disaster or other disruption were to occur in the future that affects the regions where we operate our business, our operations could be materially and adversely affected due to loss of personnel and damage to property. Even if we are not directly affected, such a disaster or disruption could affect the operations or financial conditions of our customers, which could harm our results of operations.

In addition, our business could be affected by public health epidemics and pandemics, such as the outbreak of avian influenza, severe acute respiratory syndrome, or SARS, Zika virus, Ebola virus or other diseases. In December 2019, a respiratory illness caused by a novel strain of coronavirus, SARS-CoV2, causing the Coronavirus Disease 2019, also known as COVID-19 or coronavirus, emerged. As COVID-19 has evolved into a worldwide health crisis, it has resulted in adverse effects in the global economy and financial markets, such as significant declines in the global stock markets. If the COVID-19 outbreak is not effectively controlled globally, our business and results of operations could be adversely affected to the extent the COVID-19 outbreak harms the Chinese or world economy generally. The extent to which the COVID-19 outbreak impacts our financial condition and results of operations for the full year of 2023 cannot be reasonably estimated at this time and will depend on future developments that currently cannot be predicted, including the development of a COVID-19 vaccine and the actions taken to contain the COVID-19 outbreak, among others. Any future outbreak of public health epidemics may restrict economic activities in affected regions, disrupt our business operations and adversely affect our results of operations.

The COVID-19 pandemic could adversely impact our business, including our clinical trials.

The spread of the COVID-19 coronavirus in many countries continues to adversely impact global economic activity and has contributed to significant volatility and negative pressure in financial markets and supply chains. The pandemic has had, and could have a significantly greater, material adverse effect on the global economy. The pandemic has resulted in government authorities implementing numerous measures to try to contain the virus, such as travel bans and restrictions, quarantines, shelter-in-place or stay-at-home orders, and business shutdowns. The pandemic has also resulted, and may continue to result for an extended period, in significant disruption of global financial markets, which may reduce our ability to access capital in the future, which could negatively affect our liquidity.

The COVID-19 pandemic has adversely affected the clinical development of our product candidates. Our clinical development program timelines could continue to be negatively affected by COVID-19, which could materially and adversely affect our business, financial condition, and results of operations. Further, due to "shelter in place" orders and other public health guidance measures, we have been required to implement a work-from-home policy from time to time for certain staff members in our Suzhou site excluding those necessary to maintain minimum basic operations. In such an instance, our increased reliance on personnel working from home may negatively impact productivity, or disrupt, delay or otherwise adversely impact our business. For example, with our personnel working from home, some of our research activities that require our personnel to be in our laboratories may be delayed.

The COVID-19 pandemic may impact our workforce, supply chains or distribution networks or otherwise impact our ability to restock our medical device and supply inventories and depending upon the severity of the COVID-19 pandemic's continued spread in the United States and other countries, we may experience disruptions that could severely impact our business and clinical trials, including:

- limitation of company operations, including work from home policies and office closures;
- one or more key officers and/or employees could contract COVID-19 or otherwise be adversely affected by the virus;
- delays or difficulties in receiving deliveries of critical experimental materials;
- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation or expansion, including difficulties in recruiting clinical site investigators and clinical site staff;
- increased rates of patients withdrawing from our clinical trials following enrollment as a result of contracting COVID-19 or other health conditions or being forced to quarantine;
- delays or disruptions in preclinical experiments and IND-enabling studies due to restrictions of on-site staff and unforeseen circumstances at contract research organizations, or CROs, and vendors;
- interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others;
- changes in regulations as part of a response to the COVID-19 pandemic, which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue the clinical trials altogether;

- delays in necessary interactions with regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government or contractor personnel;
- refusal of the FDA or other regulatory authorities to accept data from clinical trials in affected geographies;
- difficulties in obtaining inspections at foreign manufacturing sites that could delay approvals; and
- limitations in employee resources that would otherwise be focused on our business, including the conduct of our clinical trials, such as because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people.

The global outbreak of the COVID-19 coronavirus continues to rapidly evolve. The extent to which the COVID-19 coronavirus may impact our business and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the outbreak, travel restrictions and social distancing in China, the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the disease.

We have limited insurance coverage, and any claims beyond our insurance coverage may result in us incurring substantial costs and a diversion of resources.

We maintain insurance policies that are required under PRC laws and regulations as well as insurance based on our assessment of our operational needs and industry practice. We also maintain liability insurance covering our clinical trials as well as maintain key-man insurance policy. In line with industry practice in the PRC, we have elected not to maintain certain types of insurances, such as business interruption insurance. Our insurance coverage may be insufficient to cover any claim for product liability, damage to our fixed assets or employee injuries. Any uninsured risks may result in substantial costs and the diversion of resources, which could adversely affect our results of operations and financial condition.

We have adopted a share incentive plan and will continue to grant share-based awards in the future, which may increase expenses associated with share-based compensation. Exercise of the awards granted will increase the number of our outstanding ordinary shares, which may adversely affect the market price of our ADSs.

We adopted the Second Amended and Restated Share Incentive Plan in December 2019 and the 2021 Performance Incentive Plan in January 2021, which we refer to as the 2019 Plan and the 2021 Plan, respectively, in this annual report, to enhance our ability to attract and retain exceptionally qualified individuals and to encourage them to acquire a proprietary interest in the growth and performance of us. We have terminated the authority to grant additional awards under the 2019 Plan and all future awards will be granted under the 2021 Plan. Therefore, the effective maximum number of shares issuable under the 2019 Plan is 10,125,726. A total of 2,994,000 of our ordinary shares was authorized for issuance with respect to awards granted under the 2021 Plan. As of March 31, 2023, the aggregate number of our ordinary shares underlying our outstanding awards under the 2019 Plan was 2,714,814. As of March 31, 2023, we have granted 3,979,160 shares awards under the 2021 Plan, excluding awards that were forfeited, cancelled or exercised after the relevant grant dates. See “Item 6 Directors, Senior Management and Employees—Share Incentive Plan.” We believe the granting of share-based awards is of significant importance to our ability to attract and retain key personnel and employees, and we will continue to grant share-based compensation to employees in the future. As a result, our expenses associated with share-based compensation may increase, which may have an adverse effect on our results of operations.

Our employees, third-party suppliers, consultants and commercial partners may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, third-party suppliers, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the NMPA and overseas regulators that have jurisdictions over us, comply with healthcare fraud and abuse laws and regulations in China and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing, and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. We currently have a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and our code of conduct and the other precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses, or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could result in the imposition of significant civil, criminal and administrative penalties, including, without limitation, damages, monetary fines, individual imprisonment, disgorgement of profits, contractual damages, reputational harm, diminished profits and future earnings, additional reporting or oversight obligations if we become subject to a corporate integrity agreement or other agreement to resolve allegations of noncompliance with the law and curtailment or restructuring of our operations, which could have a significant impact on our business. Whether or not we are successful in defending against such actions or investigations, we could incur substantial costs, including legal fees and divert the attention of management in defending ourselves against any of these claims or investigations.

We may be subject to liability lawsuits arising from our clinical trials.

We currently carry liability insurance covering our clinical trials. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or which is in excess of the limits of our insurance coverage. Our insurance policies also contain various exclusions, and we may be subject to particular liability claims for which we have no coverage. We will have to pay any amount awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. In addition, if we cannot successfully defend ourselves against such claims, we may incur substantial liabilities and be required to suspend or delay our ongoing clinical trials. Even a successful defense would require significant financial and management resources.

Regardless of the merits or eventual outcome, liability claims may result in significant negative consequences to our business and prospects, including, but not limited to:

- decreased demand for our product candidates or any resulting products;
- damage to our reputation;
- withdrawal of other clinical trial participants;
- costs to defend the related litigation;
- a diversion of our management’s time and resources;
- substantial monetary awards to trial participants or patients;
- inability to commercialize our product candidates; and
- a decline in the market price of our ADSs.

We are subject to changing law and regulations regarding regulatory matters, corporate governance and public disclosure that have increased both our costs and the risk of noncompliance.

We are subject to rules and regulations by various governing bodies, including, for example, the FDA, the NMPA, the SEC, which is charged with the protection of investors and the oversight of companies whose securities are publicly traded, and the various regulatory authorities in China, the United States, the EU, the Cayman Islands, and to new and evolving regulatory measures under applicable law. Our efforts to comply with new and changing laws and regulations have resulted in and are likely to continue to result in, increased general and administrative expenses and a diversion of management time and attention from revenue-generating activities to compliance activities.

Moreover, because these laws, regulations and standards are subject to varying interpretations, their application in practice may evolve over time as new guidance becomes available. This evolution may result in continuing uncertainty regarding compliance matters and additional costs necessitated by ongoing revisions to our disclosure and governance practices. If we fail to address and comply with these regulations and any subsequent changes, we may be subject to penalties and our business may be harmed.

We may be exposed to liabilities under the U.S. Foreign Corrupt Practices Act and Chinese anti-corruption laws, and any determination that we have violated these laws could have a material adverse effect on our business or our reputation.

We are subject to anti-bribery laws in China that generally prohibit companies and their intermediaries from making payments to government officials for the purpose of obtaining or retaining business or securing any other improper advantage. In addition, although currently our primary operating business is in China, we are subject to the Foreign Corrupt Practices Act, or the FCPA. The FCPA generally prohibits us from making improper payments to non-U.S. officials for the purpose of obtaining or retaining business. We are also subject to the anti-bribery laws of other jurisdictions, particularly China. As our business expands, the applicability of the FCPA and other anti-bribery laws to our operations will increase. Our procedures and controls to monitor anti-bribery compliance may fail to protect us from reckless or criminal acts committed by our employees or agents. If we, due to either our own deliberate or inadvertent acts or those of others, fail to comply with applicable anti-bribery laws, our reputation could be harmed and we could incur criminal or civil penalties, other sanctions and/or significant expenses, which could have a material adverse effect on our business, including our financial condition, results of operations, cash flows and prospects.

Any failure to comply with applicable regulations and industry standards or obtain various licenses and permits could harm our reputation, business, results of operations and prospects.

A number of governmental agencies or industry regulatory bodies in China, the United States and other applicable jurisdictions impose strict rules, regulations and industry standards governing biopharmaceutical research and development activities, which apply to us. Our or our CROs' failure to comply with such regulations could result in the termination of ongoing research, administrative penalties imposed by regulatory bodies or the disqualification of data for submission to regulatory authorities. This could harm our business, reputation, prospects for future work and results of operations. For example, if we or our CROs were to treat research animals inhumanely or in violation of international standards set out by the Association for Assessment and Accreditation of Laboratory Animal Care, it could revoke any such accreditation and the accuracy of our animal research data could be questioned.

If we or our third-party research collaborators or other contractors or consultants fail to comply with environmental, fire protection, drainage or health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We and third parties, such as our CROs, are subject to numerous environmental, fire protection, drainage or health and safety laws and regulations, including but not limited to those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes discharge of stationary pollution sources. The cost of compliance with health and safety regulations is substantial. Our business activities involve the controlled use of hazardous materials. Our research and development activities involve the controlled storage, use and disposal of hazardous materials, including the components of our product candidates and other hazardous compounds. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials, which could cause an interruption of our commercialization efforts, research and development efforts and business operations. We cannot guarantee that the safety procedures utilized by our partners and by third-party manufacturers and suppliers with whom we may contract will comply with the standards prescribed by laws and regulations or will eliminate the risk of accidental contamination or injury from these materials. In such an event, we could be held liable for any resulting damages, and such liability could exceed our resources. In addition, we may be required to incur substantial costs to comply with current or future environmental, health and safety laws and regulations which are complex, change frequently and have tended to become more stringent. We do not currently carry biological or hazardous waste insurance coverage. In the event of an accident or environmental discharge, we may be held liable for any consequential damage and any resulting claims for damages, which may exceed our financial resources and may materially adversely affect our business, financial condition, results of operations and future growth prospects, and the value of our ADSs.

Security breaches, loss of data, and other disruptions could compromise sensitive information related to our business or prevent us from accessing critical information and expose us to liability, which could adversely affect our business and our reputation.

In the ordinary course of our business, we collect and store preclinical trial data and clinical trial data which could be sensitive, including research and development information, health-related information, personally identifiable information, intellectual property, and proprietary business information owned or controlled by ourselves or other parties. We manage and maintain our applications and data utilizing a combination of on-site systems and cloud-based application systems. We utilize external security and infrastructure vendors to manage parts of our data centers. We also communicate sensitive data with third parties. We face a number of risks relative to protecting this critical information, including material system failure or security breach, loss of access risk, inappropriate use or disclosure, inappropriate modification, and the risk of our being unable to adequately monitor, audit, and modify our controls over our critical information. This risk extends to the third-party vendors and subcontractors we use to manage this sensitive data and third-party collaborators who share with us sensitive data.

Despite the implementation of security measures to protect sensitive data from unauthorized access, use or disclosure, our information technology and infrastructure may be vulnerable to attacks by hackers or viruses or breached due to employee error, malfeasance, or other malicious or inadvertent disruptions that could result in unauthorized access to, use or disclosure of, corruption of, or loss of sensitive, and/ or proprietary data, including health-related and other personal information, and could subject us to significant liabilities and regulatory and enforcement actions, and reputational damage. The COVID-19 pandemic is generally increasing the attack surface available to criminals, as more companies and individuals work online and work remotely, and as such, the risk of a cybersecurity incident potentially occurring, and our investment in risk mitigations against such an incident, is increasing. For example, there has been an increase in phishing and spam emails as well as social engineering attempts from “hackers” hoping to use the COVID-19 pandemic to their advantage. In addition, while we have implemented security measures to prevent unauthorized access to patient data, such data is currently accessible through multiple channels, and there is no guarantee we can protect our data from breach. Unauthorized access, loss, or dissemination could also result in delays of our product development and regulatory approval efforts as well as damage our reputation.

For example, the loss of clinical trial data from completed or ongoing clinical trials could result in delays in any regulatory approval or clearance efforts and significantly increase our costs to recover or reproduce the data, and subsequently commercialize the product. If we or our third-party collaborators, consultants, contractors, suppliers, or service providers were to suffer an attack or breach, for example, that resulted in the unauthorized access to or use or disclosure of health-related or other personal information, we may have to notify consumers, partners, collaborators, government authorities, and the media, and may be subject to investigations, civil penalties, administrative and enforcement actions, and litigation, any of which could harm our business and reputation. Likewise, we rely on our third-party research institution collaborators and other third parties to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business.

Our insurance policies may not be adequate to compensate us for the potential losses arising from such disruptions, failure, or security breach. In addition, such insurance may not be available to us in the future on economically reasonable terms, or at all. Further, our insurance may not cover all claims made against us and defending a suit, regardless of its merit, could be costly, divert management attention, and harm our reputation.

We are subject to existing or future foreign laws and regulations related to privacy or data security, which could lead to government enforcement actions, including civil or criminal fines or penalties, private litigation, other liabilities, and/or adverse publicity. Compliance or the failure to comply with such laws could increase the costs of our products and services, limit their use or adoption, and otherwise negatively affect our operating results and business.

In the United States, we and our partners may be subject to state and federal laws and regulations that govern data privacy, protection and security. Numerous laws and regulations, including security breach notification laws, health information privacy laws, and consumer protection laws, govern the collection, use, disclosure and protection of health-related and other personal information. In addition, we may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under the Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, and regulations implemented thereunder (collectively, “HIPAA’’). Depending on the facts and circumstances, we could be subject to criminal penalties if we knowingly obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

Even when HIPAA does not apply, according to the Federal Trade Commission, or the FTC, violating consumers’ privacy rights or failing to take appropriate steps to keep consumers’ personal information secure may constitute unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act. The FTC expects a company’s data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities. Individually identifiable health information is considered sensitive data that merits stronger safeguards.

In addition, certain state and non-U.S. laws, such as the European Union General Data Protection Regulation, or the GDPR, govern the privacy and security of health information and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. Failure to comply with these laws, where applicable, can result in the imposition of significant civil and/or criminal penalties and private litigation. For example, California enacted legislation, the California Consumer Privacy Act, or CCPA, which went into effect January 1, 2020. The CCPA, among other things, creates new data privacy obligations for covered companies and provides new privacy rights to California residents, including the right to opt out of certain disclosures of their information. The CCPA also creates a private right of action with statutory damages for certain data breaches, thereby potentially increasing risks associated with a data breach. In Europe, the GDPR went into effect in May 2018 and introduces strict requirements for processing the personal data of individuals within the EU, and the European Economic Area, or the EEA. In addition, the GDPR increases the scrutiny of transfers of personal data from clinical trial sites located in the EEA to the United States and other jurisdictions that the European Commission does not recognize as having "adequate" data protection laws, and recent legal developments in Europe have created complexity and compliance uncertainty regarding certain transfers of personal data from the EEA. For example, on July 16, 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-US Privacy Shield Framework, or Privacy Shield, under which personal data could be transferred from the EU and the EEA to United States entities who had self-certified under the Privacy Shield scheme. Moreover, it is uncertain whether the standard contractual clauses will also be invalidated by the European courts or legislature. Companies that must comply with the GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to A20 million or 4% of the annual global revenues of the noncompliant company, whichever is greater. Additionally, following Brexit, companies will have to comply with the GDPR and the GDPR as incorporated into United Kingdom national law, the latter regime having the ability to separately fine up to the greater of £17.5 million or 4% of global turnover. The relationship between the U.K. and the EU in relation to certain aspects of data protection law remains unclear, for example around how data can lawfully be transferred between each jurisdiction, which exposes us to further compliance risk.

Given the variability and evolving state of these laws, we face uncertainty as to the exact interpretation of the new requirements, and we may be unsuccessful in implementing all measures required by regulators or courts in their interpretation.

We expect that we will continue to face uncertainty as to whether our efforts to comply with evolving obligations under global data protection, privacy and security laws will be sufficient. Any failure or perceived failure by us to comply with applicable laws and regulations could result in reputational damage or proceedings or actions against us by governmental entities, individuals or others. These proceedings or actions could subject us to significant civil or criminal penalties and negative publicity, result in the delayed or halted transfer or confiscation of certain personal information, require us to change our business practices, increase our costs and materially harm our business, prospects, financial condition and results of operations. In addition, our current and future relationships with customers, vendors, pharmaceutical partners and other third parties could be negatively affected by any proceedings or actions against us or current or future data protection obligations imposed on them under applicable law, including the GDPR. In addition, a data breach affecting personal information, including health information, could result in significant legal and financial exposure and reputational damage that could potentially have an adverse effect on our business.

Business disruptions could seriously harm our future revenue, increase our costs and expenses, and have adverse effect on our financial condition.

Our operations and third parties with which we have collaborations could be subjected to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or man-made disasters or business interruptions, for which we are predominantly self-insured. In addition, we partially rely on our CROs for conducting research and development, and they may be affected by government shutdowns or withdrawn funding. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses.

Although we maintain incident management and disaster response plans, in the event of a major disruption caused by a natural disaster or man-made problem, such as power disruptions, computer viruses, data security breaches or terrorism, we may be unable to continue our operations and may endure system interruptions, reputational harm, delays in our development activities, lengthy interruptions in service, breaches of data security and loss of critical data, any of which could adversely affect our business, results of operations and financial condition.

If we fail to implement and maintain an effective system of internal controls, we may be unable to accurately or timely report our results of operations or prevent fraud, and investors' confidence and the market price of our ADSs may be materially and adversely affected.

The SEC, as required by Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, adopted rules requiring most public companies to include a management report on such company's internal control over financial reporting in its annual report, which contains the management's assessment of the effectiveness of the company's internal control over financial reporting. In addition, when a company meets the SEC's criteria, an independent registered public accounting firm must report on the effectiveness of the company's internal control over financial reporting.

We are a public company in the United States subject to the Sarbanes-Oxley Act of 2002. Our management conducted an evaluation of the effectiveness of our internal control over financial reporting and concluded that our internal control over financial reporting was effective as of December 31, 2022. For details, see "Item 15. Controls and Procedures—Remediation of Previously Reported Material Weaknesses in Internal Control over Financial Reporting."

However, we cannot assure you that in the future our management or, if applicable, our independent registered public accounting firm will not identify material weaknesses during the Section 404 of the Sarbanes-Oxley Act audit process. In addition, because of the inherent limitations of internal control over financial reporting, including the possibility of collusion or improper management override of controls, material misstatements due to error or fraud may not be prevented or detected on a timely basis. If we fail to achieve and maintain an effective internal control environment, we could suffer material misstatements in our financial statements and fail to meet our reporting obligations, which would likely cause investors to lose confidence in our reported financial information. This could in turn limit our access to capital markets, harm our results of operations, and lead to a decline in the trading price of the ADSs. Additionally, ineffective internal control over financial reporting could expose us to increased risk of fraud or misuse of corporate assets and subject us to potential delisting from the stock exchange on which we list, regulatory investigations and civil or criminal sanctions. Furthermore, we have incurred and expect to continue to incur considerable costs and to use significant management time and the other resources in an effort to comply with Section 404 and other requirements of the Sarbanes-Oxley Act, which can significantly divert our management's attention from operating our business.

If we fail to achieve and maintain an effective internal control environment, we could suffer material misstatements in our financial statements and fail to meet our reporting obligations, which would likely cause investors to lose confidence in our reported financial information. This could in turn limit our access to capital markets, harm our results of operations, and lead to a decline in the trading price of our ADSs. Additionally, ineffective internal control over financial reporting could expose us to increased risk of fraud or misuse of corporate assets and subject us to potential delisting from the Nasdaq, regulatory investigations and civil or criminal sanctions.

Risks Related to Our Intellectual Property

It is difficult and costly to protect our proprietary rights and technology, and we may not be able to protect our intellectual property rights throughout the world.

Our commercial success will depend, in part, on our ability to obtain, maintain and defend patent and other intellectual property protection (including trademarks and trade secrets) with respect to our product candidates. We cannot be certain that patents will be issued or granted with respect to our patent applications that are currently pending, or that issued or granted patents will not later be found to be invalid and/or unenforceable, be interpreted in a manner that does not adequately protect our product candidates, or otherwise provide us with any competitive advantage. Additionally, the patent applications in respect of patents licensed under our in-license arrangements may not be issued or granted, and as a result, we may not be able to have adequate protection with respect to such patents.

The patent position of biotechnology and pharmaceutical companies is generally uncertain because it involves complex legal and factual considerations. Patent applications we have filed may not be granted or issued as valid enforceable patents. Moreover, some of our patents and patent applications may in the future be, co-owned with third parties. If we are unable to obtain an exclusive license to any such third-party co-owned interest in such patents or patent applications, such co-owners may be able to license or transfer their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects. As such, we do not know the degree of future protection that we will have on our product candidates and technology, if any, and a failure to obtain adequate intellectual property protection with respect to our product candidates could have a material adverse impact on our business.

Composition-of-matter patents on the active pharmaceutical ingredient are generally considered to be the strongest form of intellectual property protection for pharmaceutical products, as such patents provide protection without regard to any method of use. Method-of-use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our products for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products “off-label.” Although off-label prescriptions may infringe or contribute to the infringement of method-of use patents, the practice is common and such infringement is difficult to prevent or prosecute. We endeavor to seek composition-of-matter patent protection for all of our product candidates. Where appropriate, we also seek method-of-use patents and patents protecting other aspects of our product candidates, including processes for discovery and manufacturing.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. The issuance of a patent is not conclusive as to its scope, validity or enforceability, and our owned and in-licensed patents may be challenged in the courts or patent offices in the PRC and abroad. For example, we may become involved in opposition, interference, derivation, inter partes review or other similar proceedings challenging our patent rights, and the outcome of any proceedings are highly uncertain. Such challenges may result in the patent claims of our owned or in-licensed patents being narrowed, invalidated or held unenforceable, which could limit our ability to stop or prevent us from stopping others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours or otherwise provide us with a competitive advantage.

Despite the measures we can take to increase our likelihood of obtaining patent and other intellectual property protections with respect to our product candidates, there can be no assurance that the existence, validity, enforceability, or scope of our intellectual property rights will not be challenged by a third party, or that we can obtain sufficient scope of claim in those patents to prevent a third party from competing against our product candidates. For example, in an infringement proceeding, a court may hold that patent rights or other intellectual property rights owned by us are invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the ground that our patent rights or other intellectual property rights do not cover the technology in question. An adverse result in any litigation proceedings could put our patent, as well as any patents that may issue in the future from our pending patent applications, at risk of being invalidated, held unenforceable or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

In addition, if we were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that our patent is invalid and/or unenforceable. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the National Intellectual Property Administration of China, or NIPA, or the applicable foreign counterpart, or made a misleading statement, during prosecution. Although we believe that we have conducted our patent prosecution in accordance with all applicable duty of candor and in good faith, the outcome following legal assertions of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Even if a defendant does not prevail on a legal assertion of invalidity and/or unenforceability, our patent claims may be construed in a manner that would limit our ability to enforce such claims against the defendant and others.

Third parties may also raise similar claims before administrative bodies in the PRC or abroad, even outside the context of litigation. Such mechanisms include ex parte re-examination, inter partes review, post-grant review, derivation and equivalent proceedings, such as opposition proceedings. Such legal proceedings could result in revocation or amendment to our patents in such a way that they no longer cover and protect our product candidates. The outcome following legal assertions of invalidity and unenforceability can be unpredictable. With respect to the validity of our patents, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we may lose part or all of the patent protection on our product candidates. Any loss of patent protection could have a material adverse impact on one or more of our product candidates and our business.

In addition to the protection afforded by patents, we seek to rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our drug discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. We may also rely on trade secret protection as temporary protection for concepts that may be included in a future patent filing. However, trade secret protection will not protect us from innovations that a competitor develops independently of our proprietary know-how. If a competitor independently develops a technology that we protect as a trade secret and files a patent application on that technology, then we may not be able to patent that technology in the future, may require a license from the competitor to use our own know-how, and if the license is not available on commercially viable terms, then we may not be able to launch our product. Although we require our employees to assign their inventions to us, and require our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot be certain that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Furthermore, the laws of different countries do not protect proprietary rights to the same extent or in the same manner as the laws of the PRC. We may encounter significant problems in protecting and defending our intellectual property both in the PRC and abroad. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, we will not be able to establish or maintain a competitive advantage in our market, and this scenario could materially adversely affect our business, financial condition and results of operations.

Moreover, trade secrets are difficult to protect, and we have limited control over the protection of trade secrets used by our collaborators and suppliers. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors, outside scientific collaborators and other advisors may unintentionally or willfully disclose our information to competitors or use such information to compete with us. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how. If our confidential or proprietary information is divulged to or acquired by third parties, including our competitors, our competitive position in the marketplace will be adversely affected and this would have a material adverse effect on our business.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain countries. The legal systems of certain countries do not favor the enforcement or protection of patents, trade secrets and other intellectual property, particularly those relating to pharmaceutical and biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in certain countries could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. We and our contractors and partners operate in certain countries that are at heightened risk of theft of technology, data and intellectual property through direct or indirect intrusion by private parties or international actors, including those affiliated with or controlled by state actors. Accordingly, our efforts to protect or enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

As is the case with other biotechnology and biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the pharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Changes in either the patent laws or interpretation of the patent laws in various countries could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. For example, patent reform legislation in the United States includes provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents via post-grant proceedings. The Leahy-Smith Act and any continuing changes in patent laws and regulations in various patent jurisdictions could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our or our collaboration partners' patent applications and the enforcement or defense of our or our collaboration partners' issued patents, all of which could harm our business, results of operations, financial condition and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain due to changes in law and courts' interpretation of the law. For example, the U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. Other courts in the United States, for example, have heightened the bar for broadly claiming antibodies. This combination of events has created uncertainty with respect to the validity and enforceability of patents, once obtained. Additionally, there are periodic proposals for changes to the patent laws of China, United States and other countries that, if adopted, could impact our ability to enforce our proprietary technology. Depending on future actions by the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our existing patent portfolio and weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

Similarly in China, intellectual property laws are constantly evolving, with efforts being made to improve intellectual property protection in China. For example, according to the Patent Law of the PRC which was latest amended in June 2021, in order to make up the time taken up by review and approval for marketing of new drugs, the patent administrative department under the State Council shall, at the request of the relevant patentee, make up the patent right duration for invention patents pertaining to new drugs that obtain the marketing authorization in China. The make-up duration shall not exceed five years, and the total valid duration of a patent right shall not exceed 14 years after a new drug is approved for marketing.

We may not be successful in obtaining or maintaining necessary rights for our development pipeline through acquisitions and licensing deals.

Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business may depend in part on our ability to acquire and maintain licenses or other rights to use these proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, or other intellectual property rights from third parties that we identify. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate, which could have a material adverse effect on our business, financial condition, results of operations and prospects for growth.

Additionally, we may sometimes collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. These institutions may provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to others, potentially blocking our ability to pursue our program. If we are unable to successfully obtain rights to required third-party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of such program and our business and financial condition could suffer.

Licensing of intellectual property involves complex legal, business and scientific issues. Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patents and other rights to third parties;
- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates, and what activities satisfy those diligence obligations;
- our right to transfer or assign the license; and
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners.

If disputes over intellectual property that we license in the future prevent or impair our ability to maintain our licensing arrangements on acceptable terms, we may not be able to successfully develop and commercialize the affected product candidates, which would have a material adverse effect on our business.

In addition, certain of our future agreements with third parties may limit or delay our ability to consummate certain transactions, may impact the value of those transactions, or may limit our ability to pursue certain activities. For example, we may in the future enter into license agreements that are not assignable or transferable, or that require the licensor's express consent in order for an assignment or transfer to take place.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful, and any unfavorable outcome from such litigation could limit our research and development activities and/or our ability to commercialize our product candidates.

Competitors may infringe our patent rights or misappropriate or otherwise violate our intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us, alleging that we infringed their patents. In addition, in a patent infringement proceeding, there is a risk that a court will decide that our asserted patents are invalid or unenforceable, in whole or in part, and that we do not have the right to stop the others from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the others from using the invention at issue on the grounds that our patents do not cover the alleged infringing activity or product. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties and other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive business position, business prospects, and financial condition. Similarly, if we assert trademark infringement claims, a court may determine that our asserted marks are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of our trademarks.

In any litigation involving our intellectual property, the award of monetary damages we receive may not be commercially valuable or even sufficient to cover our cost of bringing such action. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a material adverse effect on the price of our ADSs. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

Our commercial success depends significantly on our ability to operate without infringing upon, misappropriating or otherwise violating the intellectual property rights of third parties.

The life sciences industry is subject to rapid technological change and substantial litigation regarding patent and other intellectual property rights. Our potential competitors in both the PRC and abroad, may have substantially greater resources than us and are likely to make substantial investments in patent portfolios and competing technologies, and may apply for or obtain patents that could prevent, limit or otherwise interfere with our ability to make, use and sell our products. Numerous third-party patents exist in fields relating to our products and technologies, and it is difficult for industry participants, including us, to identify all third-party patent rights relevant to our products and technologies. Moreover, because some patent applications are maintained as confidential for a certain period of time, we cannot be certain that third parties have not filed patent applications that will cover our products and technologies if they issue as patents.

Patents could be issued to third parties that we may ultimately be found to infringe. Third parties may have or obtain valid and enforceable patents or proprietary rights that could block us from using our technology. Our failure to obtain or maintain a license from third parties to any technology that we require may materially harm our business, financial condition and results of operations. Furthermore, we would be exposed to a threat of litigation.

Third-party intellectual property right holders may also actively bring infringement or other intellectual property-related claims against us, even if we have received patent protection for our technologies, products, and services. Regardless of the merit of third parties claims against us for infringement, misappropriation or violations of their intellectual property rights, such third parties may seek and obtain injunctive or other equitable relief, which could effectively block our ability to perform clinical trials or develop, manufacture or sell our products. Further, if a patent infringement suit were brought against us, we could be forced to temporarily or permanently stop or delay our development or regulatory approval process or other activities that are the subject of such suit. Defense of these claims, even if such claims are resolved in our favor, could cause us to incur substantial expenses and be a substantial diversion of our employee resources even if we are ultimately successful. Any adverse ruling or perception of an adverse ruling in defending ourselves could have a material adverse impact on our cash position and stock price. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing, or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a material adverse effect on the price of our ADSs. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock. The occurrence of any of these events may have a material adverse effect on our business, results of operation, financial condition or cash flows.

Obtaining and maintaining patent protection depend on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent authorities, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The NIPA, and various foreign governmental patent agencies including the USPTO, JPO, and EPO require compliance with a number of procedural, documentary, fee payment and other provisions during the patent application and prosecution process. Periodic maintenance fees, renewal fees, annuity fees, and various other governmental fees on patents and/or applications will be due to be paid to the NIPA and various other governmental patent agencies outside of China in several stages over the lifetime of the patents and/or applications. We employ reputable professionals and rely on such third parties to help us comply with these requirements and effect payment of these fees with respect to the patents and patent applications that we own. Noncompliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official communications within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case, which could have a material adverse effect on our competitive position, business, financial condition, results of operations, and prospects.

We may not enter into invention assignment and confidentiality agreements with all of our employees and third parties and such agreements may not prevent ownership disputes or unauthorized disclosure of trade secrets and other proprietary information.

We rely in part upon unpatented or unpatentable trade secrets, know-how and continuing technological innovation to develop and maintain our competitive position, which we seek to protect, in part, by entering into agreements, including confidentiality agreements and non-disclosure agreements, with parties that have a need for access to them, such as certain of our employees, consultants, academic institutions, corporate partners and, other third-party service providers. Nevertheless, there can be no guarantee that an employee or a third party will not make an unauthorized use or disclosure of our proprietary confidential information. This might happen intentionally or inadvertently. It is possible that a competitor will gain access to such information and make use of such information, and that our competitive position will be compromised, in spite of any legal action we might take against persons making such unauthorized disclosures. In addition, to the extent that our employees, consultants or contractors use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Trade secrets are difficult to protect. Although we use reasonable efforts to protect our trade secrets, our employees, consultants, contractors or business partners might intentionally or inadvertently disclose our trade secret information to competitors or our trade secrets may otherwise be misappropriated. Enforcing a claim that a third party illegally obtained and is using any of our trade secrets is expensive and time consuming, and the outcome is unpredictable.

We sometimes engage individuals or research institutions to conduct research relevant to our business. The ability of these individuals or research institutions to publish or otherwise publicly disclose data and other information generated during the course of their research is subject to certain contractual limitations. These contractual provisions may be insufficient or inadequate to protect our confidential information. If we do not apply for patent protection prior to such publication, or if we cannot otherwise maintain the confidentiality of our proprietary technology and other confidential information, then our ability to obtain patent protection or to protect our trade secret information may be jeopardized, which could adversely affect our business, financial condition and results of operations.

We also seek to enter agreements with our employees and consultants that obligate them to assign any inventions created during their work for us to us. However, we may not obtain these agreements in all circumstances and the assignment of intellectual property under such agreements may not be self-executing. And it is possible that technology relevant to our business will be independently developed by a person that is not a party to such an agreement. Furthermore, if the employees and consultants who are parties to these agreements breach or violate the terms of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets and inventions through such breaches or violations. Any of the foregoing could have a material and adverse effect on our business, financial condition and results of operations.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

Some of our employees and consultants were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and our specific personnel.

We may be subject to claims challenging the inventorship of our patents and other intellectual property.

We may be subject to claims that former employees, collaborators or other third parties have an interest in our patents, trade secrets, or other intellectual property as an inventor or co-inventor. For example, we may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our product candidates. Also, former employees may become employed by competitors who develop similar technology, and could assist the competitor in designing around our patents. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Our and their assignment agreements may not be self-executing or may be breached, and litigation may be necessary to defend against these and other claims challenging inventorship or our ownership of our patents, trade secrets or other intellectual property. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

Intellectual property rights do not necessarily protect us from all potential threats to our competitive advantages.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- others may be able to independently develop similar or alternative technologies or designs that are similar to our product candidates but that are not covered by the claims of the patents that we own or have exclusively licensed;
- we might not have been the first to make the inventions covered by the issued patents or pending patent applications that we own or may in the future exclusively license, which could result in the patent applications not issuing or being invalidated after issuing;
- we might not have been the first to file patent applications covering certain of our inventions, which could result in the patent applications not issuing or being invalidated after issuing;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our pending patent applications will not lead to issued patents;
- issued patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive services and products for commercialization in our major markets;
- we may fail to develop additional proprietary technologies that are patentable;
- we may fail to apply for or obtain adequate intellectual property protection in all the jurisdictions in which we operate; and
- the patents of others may have an adverse effect on our business, for example by preventing us from commercializing one or more of our product candidates for one or more indications.

Any of the aforementioned threats to our competitive advantage could have a material adverse effect on our business.

Patent terms may not be sufficient to effectively protect our product candidates.

In most countries in which we plan to file applications for patents, the term of an issued patent is generally 20 years from the earliest claimed filing date of the priority application to which a non-provisional patent application in the applicable country claims priority. Although various extensions may be available in various countries, the life of a patent and the protection it affords are limited. Even if patents covering our product candidates are obtained, we may be open to competition from other companies once our patent rights expire. Accordingly, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Excluding any patent term adjustment and patent term extension, our currently issued patents are expected to expire from 2033 to 2038. As a result, our patent portfolio may not provide us with sufficient rights over a sufficient length of time to exclude others from commercializing products similar or identical to ours.

Uncertainty of the length of patent term extensions and data and market exclusivities for our pharmaceutical products could increase the risk of generic competition.

In the United States, the Federal Food, Drug, and Cosmetic Act, as amended by the law generally referred to as the "Hatch-Waxman Amendments," provides the opportunity for patent-term restoration of up to five years to reflect patent term lost during certain portions of product development and the FDA regulatory review process. The Hatch-Waxman Amendments also have a process for patent linkage, pursuant to which FDA will stay approval of certain follow-on applications during the pendency of litigation between the follow-on applicant and the patent holder or licensee, generally for a period of 30 months. Finally, the Hatch-Waxman Amendments provide for statutory exclusivities that can prevent submission or approval of certain follow-on marketing applications. For example, federal law provides a five-year period of exclusivity within the United States to the first applicant to obtain approval of a new chemical entity (as defined) and three years of exclusivity protecting certain innovations to previously approved active ingredients where the applicant was required to conduct new clinical investigations to obtain approval for the modification. Similarly, the Orphan Drug Act provides seven years of market exclusivity for certain drugs to treat rare diseases, where FDA designates the product candidate as an orphan drug and the drug is approved for the designated orphan indication.

These provisions, designed to promote innovation, can prevent competing products from entering the market for a certain period of time after FDA grants marketing approval for the innovative product.

In China, however, there is no currently effective law or regulation providing patent term extension, patent linkage, or data exclusivity (referred to as regulatory data protection). Therefore, a lower-cost generic drug can emerge onto the market much more quickly. Chinese regulators have set forth a framework for integrating patent linkage and data exclusivity into the Chinese regulatory regime, as well as for establishing a pilot program for patent term extension. To be implemented, this framework will require adoption of regulations. To date, the NMPA has issued several draft implementing regulations in this regard for public comment but no regulations have been formally issued. These factors result in weaker protection for us against generic competition in China than could be available to us in the United States until the relevant implementing regulations for extension, patent linkage, or data exclusivity are put into effect officially in China.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on our products in all countries throughout the world would be prohibitively expensive. We may also encounter difficulties in protecting and defending such rights in foreign jurisdictions. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the jurisdictions of the registration of our intellectual properties. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products. Our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in certain jurisdictions. The legal systems of many other countries do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents in such countries.

Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

We may not be able to protect and enforce our trademarks.

We currently hold issued trademark registrations and have trademark applications pending, any of which may be the subject of a governmental or third-party objection, which could prevent the registration or maintenance of the same. If we are unsuccessful in obtaining trademark protection for our primary brands, we may be required to change our brand names, which could materially adversely affect our business. Moreover, as our products mature, our reliance on our trademarks to differentiate us from our competitors will increase, and as a result, if we are unable to prevent third parties from adopting, registering or using trademarks and trade dress that infringe, dilute or otherwise violate our trademark rights, or engaging in conduct that constitutes unfair competition, defamation or other violation of our rights, our business could be materially adversely affected. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. We may license our trademarks and trade names to third parties, such as distributors. Though these license agreements may provide guidelines for how our trademarks and trade names may be used, a breach of these agreements or misuse of our trademarks and tradenames by our licensees may jeopardize our rights in or diminish the goodwill associated with our trademarks and trade names. Our efforts to enforce or protect our proprietary rights related to trademarks, trade names, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely affect our financial condition or results of operations.

Risks Related to the ADSs

Our business and financial results, including our ability to raise capital or raise capital on favorable terms and the market price of our ADSs, may be adversely affected by the geopolitical factors arising in connection with Russia's invasion of Ukraine, including particularly how countries like the United States and China choose to respond to this war. As a result, the value of our ADSs may significantly decline.

Our business and financial results, including our ability to raise capital or raise capital on favorable terms and the market price of our ADSs, may be adversely affected by the geopolitical factors arising in connection with Russia's invasion of Ukraine. We do not conduct business in either Russia or Ukraine. However, our global operations expose us to geopolitical risks, including particularly here, how the United States and China choose to respond to the war between Ukraine and Russia. If this war continues, increases, or expands, or leads to continued political or economic instability, terrorist activity, or gives rise to further government actions such as sanctions or increased economic or political tensions between the United States and China, our business and financial results, including our ability to raise capital or raise capital on favorable terms and the market price of our ADSs, may be adversely impacted and the value of our ADSs may significantly decline.

You may be subject to limitations on transfer of your ADSs.

Your ADSs are transferable on the books of the depositary. However, the depositary may close its transfer books at any time or from time to time when it deems expedient in connection with the performance of its duties. In addition, the depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or at any time if we or the depositary deems it advisable to do so because of any requirement of law or of any government or governmental body, or under any provision of the deposit agreement, or for any other reason in accordance with the terms of the deposit agreement.

The trading price of the ADSs is likely to be volatile, which could result in substantial losses to investors.

The trading price of our ADSs ranged from US$0.90 to US$29.99 per ADS since the listing of ADSs on Nasdaq. The trading price of the ADSs is likely to be volatile and could fluctuate widely due to factors beyond our control. This may happen because of broad market and industry factors, including the performance and fluctuation of the market prices of other companies with business operations located mainly in China that have listed their securities in the United States. In addition to market and industry factors, the price and trading volume for the ADSs may be highly volatile for factors specific to our own operations, including the following:

- variations in our net revenues, earnings and cash flow;
- announcements of new investments, acquisitions, strategic partnerships, or joint ventures by us or our competitors;
- announcements of new products and services and expansions by us or our competitors;

- changes in financial estimates by securities analysts;
- fluctuations in operating metrics;
- failure on our part to realize monetization opportunities as expected;
- changes in revenues generated from our significant business partners;
- additions or departures of key personnel;
- release of lock-up or other transfer restrictions on our outstanding equity securities or sales of additional equity securities;
- detrimental negative publicity about us, our management, our competitors or our industry;
- regulatory developments affecting us or our industry; and
- potential litigation or regulatory investigations.

Any of these factors may result in large and sudden changes in the trading volume and price of the ADSs.

In the past, shareholders of public companies have often brought securities class action suits against those companies following periods of instability in the market price of their securities. If we were involved in a class action suit, it could divert a significant amount of our management's attention and other resources from our business and operations and require us to incur significant expenses to defend the suit, which could harm our results of operations. Any such class action suit, whether or not successful, could harm our reputation and restrict our ability to raise capital in the future. In addition, if a claim is successfully made against us, we may be required to pay significant damages, which could have a material adverse effect on our financial condition and results of operations.

We are an emerging growth company within the meaning of the Securities Act and may take advantage of certain reduced reporting requirements.

We are an "emerging growth company," as defined in the JOBS Act, and we may take advantage of certain exemptions from requirements applicable to other public companies that are not emerging growth companies including, most significantly, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002 for so long as we remain an emerging growth company. As a result, if we elect not to comply with such auditor attestation requirements, our investors may not have access to certain information they may deem important.

If securities or industry analysts cease to publish research or reports about our business, or if they adversely change their recommendations regarding the ADSs, the market price for the ADSs and trading volume could decline.

The trading market for the ADSs will be influenced by research or reports that industry or securities analysts publish about our business. If one or more analysts who cover us downgrade the ADSs, the market price for the ADSs would likely decline. If one or more of these analysts cease to cover us or fail to regularly publish reports on us, we could lose visibility in the financial markets, which, in turn, could cause the market price or trading volume for the ADSs to decline.

The sale or availability for sale, or perceived sale or availability for sale, of substantial amounts of the ADSs could adversely affect their market price.

Sales of substantial amounts of the ADSs in the public market, or the perception that these sales could occur, could adversely affect the market price of the ADSs and could materially impair our ability to raise capital through equity offerings in the future. The ADSs sold in our initial public offering are freely tradable by persons other than our "affiliates" without restriction or further registration under the Securities Act, and shares held by our existing shareholders may also be sold in the public market in the future subject to the restrictions in Rule 144 and Rule 701 under the Securities Act and the applicable lock-up agreements.

Our memorandum and articles of association contain anti-takeover provisions that could have a material adverse effect on the rights of holders of our ordinary shares and the ADSs.

We have adopted amended and restated memorandum and articles of association. Our new memorandum and articles of association contain provisions to limit the ability of others to acquire control of our company or cause us to engage in change-of-control transactions. These provisions could have the effect of depriving our shareholders of an opportunity to sell their shares at a premium over prevailing market prices by discouraging third parties from seeking to obtain control of our company in a tender offer or similar transaction. Our board of directors has the authority, without further action by our shareholders, to issue preferred shares in one or more series and to fix their designations, powers, preferences, privileges, and relative participating, optional or special rights and the qualifications, limitations or restrictions, including dividend rights, conversion rights, voting rights, terms of redemption and liquidation preferences, any or all of which may be greater than the rights associated with our ordinary shares, including ordinary shares represented by ADSs. Preferred shares could be issued quickly with terms calculated to delay or prevent a change in control of our company or make removal of management more difficult. If our board of directors decides to issue preferred shares, the price of the ADSs may fall and the voting and other rights of the holders of our ordinary shares and the ADSs may be materially and adversely affected.

You must rely on the judgment of our management as to the use of the net proceeds from our equity financing activities, and such use may not produce income or increase our ADS price.

Our management will have considerable discretion in the application of the net proceeds received by us. You will not have the opportunity, as part of your investment decision, to assess whether proceeds are being used appropriately. The net proceeds may be used for corporate purposes that do not improve our efforts to achieve or maintain profitability or increase our ADS price. The net proceeds from our initial public offering and other equity financing activities may be placed in investments that do not produce income or that lose value.

We are entitled to amend the deposit agreement and to change the rights of ADS holders under the terms of such agreement, or to terminate the deposit agreement, without the prior consent of the ADS holders.

We are entitled to amend the deposit agreement and to change the rights of the ADS holders under the terms of such agreement, without the prior consent of the ADS holders. We and the depositary may agree to amend the deposit agreement in any way we decide is necessary or advantageous to us. Amendments may reflect, among other things, operational changes in the ADS program, legal developments affecting ADSs or changes in the terms of our business relationship with the depositary. In the event that the terms of an amendment are disadvantageous to ADS holders, ADS holders will only receive 30 days' advance notice of the amendment, and no prior consent of the ADS holders is required under the deposit agreement. Furthermore, we may decide to terminate the ADS facility at any time for any reason. For example, terminations may occur when we decide to list our shares on a non-U.S. securities exchange and determine not to continue to sponsor an ADS facility or when we become the subject of a takeover or a going-private transaction. If the ADS facility is going to terminate, ADS holders will receive at least 90 days' prior notice, but no prior consent is required from them. Under the circumstances that we decide to make an amendment to the deposit agreement that is disadvantageous to ADS holders or terminate the deposit agreement, the ADS holders may choose to sell their ADSs or surrender their ADSs and become direct holders of the underlying ordinary shares, but will have no right to any compensation whatsoever.

ADSs holders may not be entitled to a jury trial with respect to claims arising under the deposit agreement, which could result in less favorable outcomes to the plaintiff(s) in any such action.

The deposit agreement governing the ADSs representing our ordinary shares provides that, to the fullest extent permitted by law, ADS holders waive the right to a jury trial of any claim they may have against us or the depositary arising out of or relating to our shares, the ADSs or the deposit agreement, including any claim under the U.S. federal securities laws.

If we or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable based on the facts and circumstances of that case in accordance with the applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the United States Supreme Court. However, we believe that a contractual pre-dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, by a federal or state court in the City of New York, which has non-exclusive jurisdiction over matters arising under the deposit agreement. In determining whether to enforce a contractual pre-dispute jury trial waiver provision, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this is the case with respect to the deposit agreement and the ADSs. It is advisable that you consult legal counsel regarding the jury waiver provision before entering into the deposit agreement.

If you or any other holders or beneficial owners of ADSs bring a claim against us or the depositary in connection with matters arising under the deposit agreement or the ADSs, including claims under federal securities laws, you or such other holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us or the depositary. If a lawsuit is brought against us or the depositary under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may result in different outcomes than a trial by jury would have had, including results that could be less favorable to the plaintiff(s) in any such action.

Nevertheless, if this jury trial waiver provision is not permitted by applicable law, an action could proceed under the terms of the deposit agreement with a jury trial.

No condition, stipulation or provision of the deposit agreement or ADSs serves as a waiver by any holder or beneficial owner of ADSs or by us or the depositary of compliance with any substantive provision of the U.S. federal securities laws and the rules and regulations promulgated thereunder.

The voting rights of holders of ADSs are limited by the terms of the deposit agreement, and you may not be able to exercise your right to direct the voting of the underlying ordinary shares represented by your ADSs.

Holders of ADSs do not have the same rights as our registered shareholders. As a holder of ADSs, you will not have any direct right to attend general meetings of our shareholders or to cast any votes at such meetings. You will only be able to exercise the voting rights attached to the ordinary shares underlying your ADSs indirectly by giving voting instructions to the depositary in accordance with the provisions of the deposit agreement. Where any matter is to be put to a vote at a general meeting, then upon receipt of your voting instructions, the depositary will try, as far as is practicable, to vote the underlying ordinary shares represented by your ADSs in accordance with your instructions. You will not be able to directly exercise your right to vote with respect to the underlying ordinary shares unless you cancel and withdraw the shares and become the registered holder of such shares prior to the record date for the general meeting.

When a general meeting is convened, you may not receive sufficient advance notice of the meeting to withdraw the ordinary shares represented by your ADSs and become the registered holder of such shares to allow you to attend the general meeting and to vote directly with respect to any specific matter or resolution to be considered and voted upon at the general meeting. In addition, under our post-offering memorandum and articles of association, for the purposes of determining those shareholders who are entitled to attend and vote at any general meeting, our directors may close our register of members and/or fix in advance a record date for such meeting, and such closure of our register of members or the setting of such a record date may prevent you from withdrawing the underlying ordinary shares represented by your ADSs and from becoming the registered holder of such shares prior to the record date, so that you would not be able to attend the general meeting or to vote directly. Where any matter is to be put to a vote at a general meeting, upon our instruction the depositary will notify you of the upcoming vote and will arrange to deliver our voting materials to you. We cannot assure you that you will receive the voting materials in time to ensure that you can instruct the depositary to vote the underlying ordinary shares represented by your ADSs.

In addition, the depositary and its agents are not responsible for failing to carry out voting instructions or for their manner of carrying out your voting instructions. This means that you may not be able to exercise your right to direct how the underlying ordinary shares represented by your ADSs are voted and you may have no legal remedy if the underlying ordinary shares represented by your ADSs are not voted as you requested. In addition, in your capacity as an ADS holder, you will not be able to call a shareholders' meeting.

Under the deposit agreement, if you do not vote, the depositary may give us a discretionary proxy to vote the ordinary shares underlying the ADSs at shareholders' meetings if we have timely provided the depositary with notice of meeting and related voting materials and (i) we have instructed the depositary that we wish a discretionary proxy to be given, (ii) we have informed the depositary that there is no substantial opposition as to a matter to be voted on at the meeting, and (iii) a matter to be voted on at the meeting would not have a material adverse impact on shareholders.

The effect of this discretionary proxy is that you cannot prevent the underlying ordinary shares represented by the ADSs from being voted, except under the circumstances described above. This may make it more difficult for ADS holders to influence the management of the company. Holders of ordinary shares are not subject to this discretionary proxy.

Because we do not expect to pay dividends in the foreseeable future, you must rely on price appreciation of the ADSs for return on your investment.

We currently intend to retain most, if not all, of our available funds and any future earnings to fund the development and growth of our business. As a result, we do not expect to pay any cash dividends in the foreseeable future. Therefore, you should not rely on an investment in the ADSs as a source for any future dividend income.

Our board of directors has complete discretion as to whether to distribute dividends, subject to certain requirements of Cayman Islands law. In addition, our shareholders may, subject to the provisions of our articles of association, by ordinary resolution declare a dividend, but no dividend may exceed the amount recommended by our directors. Under Cayman Islands law, a Cayman Islands company may pay a dividend out of either profit, retained earnings, or share premium account, provided that in no circumstances may a dividend be paid if this would result in the company being unable to pay its debts as they fall due in the ordinary course of business. Even if our board of directors decides to declare and pay dividends, the timing, amount and form of future dividends, if any, will depend on our future results of operations and cash flow, our capital requirements and surplus, the amount of distributions, if any, received by us from our subsidiary, our financial condition, contractual restrictions and other factors deemed relevant by our board of directors. Accordingly, the return on your investment in the ADSs will likely depend entirely upon any future price appreciation of the ADSs. There is no guarantee that the ADSs will appreciate in value or even maintain the price at which you purchased the ADSs. You may not realize a return on your investment in the ADSs and you may even lose your entire investment in the ADSs.

You may not receive dividends or other distributions on our ordinary shares and you may not receive any value for them, if it is illegal or impractical to make them available to you.

The depositary has agreed to pay to you the cash dividends or other distributions it or the custodian receives on ordinary shares or other deposited securities underlying the ADSs, after deducting its fees and expenses. You will receive these distributions in proportion to the number of ordinary shares your ADSs represent. However, the depositary is not responsible if it decides that it is unlawful or impractical to make a distribution available to any holders of ADSs. For example, it would be unlawful to make a distribution to a holder of ADSs if it consists of securities that require registration under the Securities Act of 1933 but that are not properly registered or distributed under an applicable exemption from registration. The depositary may also determine that it is not feasible to distribute certain property through the mail. Additionally, the value of certain distributions may be less than the cost of mailing them. In these cases, the depositary may determine not to distribute such property. We have no obligation to register under U.S. securities laws any ADSs, ordinary shares, rights or other securities received through such distributions. We also have no obligation to take any other action to permit the distribution of ADSs, ordinary shares, rights or anything else to holders of ADSs. This means that you may not receive distributions we make on our ordinary shares or any value for them if it is illegal or impractical for us to make them available to you. These restrictions may cause a material decline in the value of the ADSs.

You may experience dilution of your holdings due to the inability to participate in rights offerings.

We may, from time to time, distribute rights to our shareholders, including rights to acquire securities. Under the deposit agreement, the depositary will not distribute rights to holders of ADSs unless the distribution and sale of rights and the securities to which these rights relate are either exempt from registration under the Securities Act with respect to all holders of ADSs, or are registered under the provisions of the Securities Act. The depositary may, but is not required to, attempt to sell these undistributed rights to third parties, and may allow the rights to lapse. We may be unable to establish an exemption from registration under the Securities Act, and we are under no obligation to file a registration statement with respect to these rights or underlying securities or to endeavor to have a registration statement declared effective. Accordingly, holders of ADSs may be unable to participate in our rights offerings and may experience dilution of their holdings as a result.

We will incur increased costs as a result of being a public company, particularly after we cease to qualify as an "emerging growth company."

We are a public company and expect to incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, as well as rules subsequently implemented by the Securities and Exchange Commission, or the SEC, and the Nasdaq Global Market, impose various requirements on the corporate governance practices of public companies. As a company with less than US$1.07 billion in revenues for our last fiscal year, we qualify as an "emerging growth company" pursuant to the JOBS Act. An emerging growth company may take advantage of specified reduced reporting and other requirements that are otherwise applicable generally to public companies. These provisions include exemption from the auditor attestation requirement under Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, in the assessment of the emerging growth company's internal control over financial reporting and permission to delay adopting new or revised accounting standards until such time as those standards apply to private companies.

We expect these rules and regulations to increase our legal and financial compliance costs and to make some corporate activities more time-consuming and costly. After we are no longer an "emerging growth company," we expect to incur significant expenses and devote substantial management effort toward ensuring compliance with the requirements of Section 404 of the Sarbanes-Oxley Act of 2002 and the other rules and regulations of the SEC. For example, as a result of becoming a public company, we will need to increase the number of independent directors and adopt policies regarding internal controls and disclosure controls and procedures. We also expect that operating as a public company will make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. In addition, we will incur additional costs associated with our public company reporting requirements. It may also be more difficult for us to find qualified persons to serve on our board of directors or as executive officers. We are currently evaluating and monitoring developments with respect to these rules and regulations, and we cannot predict or estimate with any degree of certainty the number of additional costs we may incur or the timing of such costs.

You may face difficulties in protecting your interests, and your ability to protect your rights through U.S. courts may be limited, because we are incorporated under Cayman Islands law.

We are an exempted company incorporated under the laws of the Cayman Islands with limited liability. Our corporate affairs are governed by our memorandum and articles of association, the Companies Act (as amended) of the Cayman Islands and the common law of the Cayman Islands. The rights of shareholders to take action against our directors, actions by our minority shareholders and the fiduciary duties of our directors to us under Cayman Islands law are to a large extent governed by the common law of the Cayman Islands. The common law of the Cayman Islands is derived in part from comparatively limited judicial precedent in the Cayman Islands as well as from the common law of England, the decisions of whose courts are of persuasive authority, but are not binding, on a court in the Cayman Islands. The rights of our shareholders and the fiduciary duties of our directors under Cayman Islands law are not as clearly established as they would be under statutes or judicial precedent in some jurisdictions in the United States. In particular, the Cayman Islands has a less developed body of securities laws than the United States. Some U.S. states, such as Delaware, have more fully developed and judicially interpreted bodies of corporate law than the Cayman Islands. In addition, Cayman Islands companies may not have the standing to initiate a shareholder derivative action in a federal court of the United States.

Shareholders of Cayman Islands exempted companies like us have no general rights under Cayman Islands law to inspect corporate records or to obtain copies of lists of shareholders of these companies. Our directors have discretion under our articles of association to determine whether or not, and under what conditions, our corporate records may be inspected by our shareholders, but are not obliged to make them available to our shareholders. This may make it more difficult for you to obtain the information needed to establish any facts necessary for a shareholder motion or to solicit proxies from other shareholders in connection with a proxy contest.

As a result of all of the above, our public shareholders may have more difficulties in protecting their interests in the face of actions taken by management, members of our board of directors or controlling shareholders than they would as public shareholders of a company incorporated in the United States.

Certain judgments obtained against us by our shareholders may not be enforceable.

We are a Cayman Islands exempted company and substantially all of our assets are located outside of the United States. Our current operations are primarily conducted in China. In addition, some of our current directors and officers are nationals and residents of countries other than the United States. Substantially all of the assets of these persons are located outside the United States. As a result, it may be difficult or impossible for you to bring an action against us or against these individuals in the United States in the event that you believe that your rights have been infringed under the U.S. federal securities laws or otherwise. Even if you are successful in bringing an action of this kind, the laws of the Cayman Islands and of China may render you unable to enforce a judgment against our assets or the assets of our directors and officers.

As an exempted company incorporated in the Cayman Islands, we are permitted to adopt certain home country practices in relation to corporate governance matters that differ significantly from the Nasdaq listing standards; these practices may afford less protection to shareholders than they would enjoy if we complied fully with the Nasdaq listing standards.

As a Cayman Islands exempted company listed on the Nasdaq Global Market, we are subject to the Nasdaq listing standards. However, Nasdaq rules permit a foreign private issuer like us to follow the corporate governance practices of its home country. Certain corporate governance practices in the Cayman Islands, which is our home country, may differ significantly from the Nasdaq listing standards. We have relied on and plan to rely on home country practice with respect to our corporate governance. For example, we do not have a majority of independent directors serving on our board of directors, and each of our nominating committee and compensation committee is not composed entirely of independent directors. In addition, we do not plan to seek shareholder approval in connection with certain transactions effecting securities issuance. We also do not plan to hold annual meeting of shareholders no later than one year after the end of fiscal year-end. For details, please refer to “Item 6. Directors, Senior Management and Employees—6.C. Board Practices—Board of Directors” and “Item 16G—Corporate Governance.” As a result, our shareholders may be afforded less protection than they would otherwise enjoy under the Nasdaq listing standards applicable to U.S. domestic issuers.

We are a foreign private issuer within the meaning of the rules under the Exchange Act, and as such we are exempt from certain provisions applicable to U.S. domestic public companies.

Because we qualify as a foreign private issuer under the Exchange Act, we are exempt from certain provisions of the securities rules and regulations in the United States that are applicable to U.S. domestic issuers, including:

- the rules under the Exchange Act requiring the filing with the SEC of quarterly reports on Form 10-Q or current reports on Form 8-K;
- the sections of the Exchange Act regulating the solicitation of proxies, consents or authorizations in respect of a security registered under the Exchange Act;
- the sections of the Exchange Act requiring insiders to file public reports of their stock ownership and trading activities and liability for insiders who profit from trades made in a short period of time; and
- the selective disclosure rules by issuers of material nonpublic information under Regulation FD.

We will be required to file an annual report on Form 20-F within four months of the end of each fiscal year. In addition, we have published and intend to continue to publish a summary of our financial results on a semi-annually basis as press releases, distributed pursuant to the rules and regulations of the Nasdaq Global Market. Press releases relating to financial results and material events will also be furnished to the SEC on Form 6-K. However, the information we are required to file with or furnish to the SEC will be less extensive and less timely compared to that required to be filed with the SEC by U.S. domestic issuers. As a result, you may not be afforded the same protections or information that would be made available to you were you investing in a U.S. domestic issuer.

We were likely a passive foreign investment company, or PFIC, for 2022, and there is a significant risk that we will be a PFIC for 2023 and possibly subsequent taxable years, in which case U.S. investors will generally be subject to adverse U.S. federal income tax consequences.

In general, a non-U.S. corporation will be a PFIC for any taxable year in which (i) 75% or more of its gross income consists of passive income, or the income test, or (ii) 50% or more of the average value of its assets (generally determined on a quarterly basis) consists of assets that produce, or are held for the production of, passive income, or the asset test. For purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the ordinary shares of another corporation is treated as if it held its proportionate share of the assets of the other corporation and received directly its proportionate share of the income of the other corporation. Passive income generally includes interest, dividends, gains from certain property transactions, rents and royalties (other than certain rents or royalties derived in the active conduct of a trade or business). Cash is generally a passive asset for PFIC purposes. Goodwill is an active asset under the PFIC rules to the extent attributable to activities that produce active income.

The assets shown on our balance sheet are expected to consist primarily of cash and cash equivalents for the foreseeable future. Therefore, whether we will satisfy the asset test for any taxable year will depend largely on the value of our goodwill and on how quickly we utilize the cash in our business. The value of our goodwill for any taxable year may be determined in large part by reference to the average of our market capitalization for that year. Because our market capitalization has generally declined substantially since our initial public offering (including in 2022 and recent months), if the value of our goodwill is determined by reference to the average of our quarterly market capitalization, then it is our belief that we were likely a PFIC for our 2022 taxable year. Due to our declining market capitalization, there is a significant risk that we will also be a PFIC for 2023 and possibly future taxable years. In addition, the extent to which our goodwill should be characterized as a non-passive asset is not entirely clear. We have not obtained any valuation of our assets (including goodwill). U.S. Holders of our ADSs or ordinary shares should consult their tax advisors regarding the value and characterization of our assets for purposes of the PFIC rules, which are subject to some uncertainties.

If we are a PFIC for any taxable year during which a U.S. investor owns our ADSs or ordinary shares, the U.S. taxpayer generally will be subject to adverse U.S. federal income tax consequences, including increased tax liability on disposition gains and "excess distributions," and additional reporting requirements. This will generally continue to be the case even if we ceased to be a PFIC in a later taxable year, unless certain elections are made. See "Item 10 Additional Information—Taxation—Material U.S. Federal Income Tax Consequences—Passive Foreign Investment Company Rules."

If a U.S. person is treated as owning 10% or more of our stock by vote or value, such person may be subject to adverse U.S. federal income tax consequences.

If a U.S. person is treated as owning (directly, indirectly or constructively) 10% or more of our stock (including our ADSs and ordinary shares) by value or voting power, such person generally will be treated as a "United States shareholder" with respect to each "controlled foreign corporation," or CFC, in our group. A CFC is a non-U.S. corporation more than 50% of the stock (by voting power or value) of which is owned (directly, indirectly or constructively) by "United States shareholders." We have not determined whether we are a CFC. However, even if we are not a CFC, under certain ownership attribution rules our non-U.S. subsidiaries would be treated as owned by our U.S. subsidiary and thus may be treated as CFCs. A United States shareholder of a CFC may be subject to additional U.S. federal income tax liabilities and reporting requirements. We do not intend to furnish to any information that may be necessary for United States shareholders, if any, to comply with the CFC rules. U.S. investors that may be treated for purposes of the CFC rules as owning 10% of our stock by voting power or value should consult their tax advisors regarding the potential application of these rules in their particular circumstances.

ITEM 4. INFORMATION ON THE COMPANY

4.A. History and Development of the Company

In February 2011, Adagene Inc. was incorporated under the laws of the Cayman Islands as our offshore holding company.

In December 2011, we established Adagene (Hong Kong) Limited, or Adagene Hong Kong, a wholly-owned subsidiary incorporated under the laws of Hong Kong, as our intermediary holding company. In February 2012, Adagene Hong Kong incorporated Adagene (Suzhou) Limited, or Adagene Suzhou, in China, through which we commenced our research and development activities in China.

In September 2017, we established a wholly-owned subsidiary in the state of Delaware, the United States, Adagene Incorporated, to conduct our research and development activities in the United States to facilitate the discovery and development of product candidates and expand our global presence, we have further incorporated several subsidiaries overseas, such as Australia, Singapore and Switzerland.

We are a holding company and do not directly conduct any substantive business operations in the PRC. In addition to our R&D activities in the United States, Australia and Singapore, we currently focus our business operations within the PRC through Adagene Suzhou. We (Adagene Inc.), however, hold certain intellectual properties and outsource certain research and development activities related to these intellectual properties to our subsidiaries. See “Item 3 Key Information—D. Risk Factors—Risks Related to Doing Business in the PRC.”

In February 2021, we completed an initial public offering in which we offered and sold an aggregate of 10,571,375 ordinary shares in the form of ADSs. Upon the initial public offering, all of our then issued and outstanding preferred shares were automatically converted into ordinary shares on a one-for-one basis. On February 9, 2021, the ADSs began trading on the Nasdaq under the symbol “ADAG.”

Our corporate headquarters is located at 4F, Building C14, No. 218, Xinghu Street, Suzhou Industrial Park Suzhou, Jiangsu Province, 215123, People’s Republic of China. Our San Diego office address is 10179 Huennekens Street Suite 103, San Diego, CA 92121. Our registered office is located at Vistra (Cayman) Limited, P. O. Box 31119 Grand Pavilion, Hibiscus Way, 802 West Bay Road, Grand Cayman, KY1 - 1205 Cayman Islands. Our telephone number is +86-512-8777-3632. Our agent for service of process in the United States is Cogency Global Inc., located at 122 East 42nd Street, 18th Floor, New York, NY 10168. Our corporate website is www.adagene.com. The information contained on or that can be accessed through our website is not incorporated by reference into this annual report, and you should not consider information on our website to be part of this annual report.

The SEC maintains an internet site at *www.sec.gov* that contains reports, information statements, and other information regarding issuers that file electronically with the SEC.

Recent Regulatory Development

Implication of the Holding Foreign Companies Accountable Act

The Holding Foreign Companies Accountable Act (the “HFCA Act”), was enacted on December 18, 2020. Trading in our ADSs on the Nasdaq or over-the-counter will be prohibited, and as a result, our ADSs will be delisted under the HFCA Act, if the PCAOB has determined that it has been unable to inspect registered public accounting firms headquartered in mainland China and Hong Kong for two consecutive years. The enactment of the Accelerating Holding Foreign Companies Accountable Act (“AHFCA Act”) decreases the number of non-inspection years from three years to two, thus reducing the time period before our ADSs will be prohibited from trading on the Nasdaq Stock Market or OTC or delisted. For the details of the risks associated with the enactment of the AHFCA Act, see “Item 3. Key Information––3.D. Risk Factors–– The enactment of the Accelerating Holding Foreign Companies Accountable Act decreases the number of non-inspection years from three years to two, thus reducing the time period before our ADSs may be prohibited from trading on the Nasdaq Stock Market or in the over-the-counter market or delisted.”

On December 16, 2021, PCAOB issued the HFCA Act Determination Report, according to which our auditor was subject to the determinations that the PCAOB is unable to inspect or investigate completely (the "2021 Determinaitons"). In March 2022, the SEC issued its first "Conclusive list of issuers identified under the HFCAA" indicating that those companies are now formally subject to the delisting provisions if they remain on the list for two consecutive years. We were conclusively identified on May 26, 2022. See https:// www.sec.gov/hfcaa. Our auditor, the independent registered public accounting firm that issues the audit report included elsewhere in this annual report, as an auditor of companies that are traded publicly in the United States and a firm registered with the PCAOB, is subject to laws in the United States pursuant to which the PCAOB conducts regular inspections to assess its compliance with the applicable professional standards. Since our auditor is located in China, a jurisdiction where the PCAOB had been unable to conduct inspections without the approval of the PRC authorities, our auditor was not inspected by the PCAOB. Final rules implementing the submission and disclosure requirements in the HFCA Act were adopted by the SEC on December 2, 2021 and became effective on January 10, 2022.

On August 26, 2022, the PCAOB signed a Statement of Protocol with China Securities Regulatory Commission and the Ministry of Finance of the People's Republic of China, taking the first step toward opening access for the PCAOB to inspect and investigate registered public accounting firms headquartered in mainland China and Hong Kong. On December 15, 2022, the PCAOB announced that it was able, in 2022, to inspect and investigate completely issuer audit engagements of PCAOB-registered public accounting firms headquartered in mainland China and Hong Kong and that it had vacated its 2021 Determinaitons accordingly. As a result, we do not expect to be identified as a Commission-Identified Issuer under the HFCA Act for the fiscal year ended December 31, 2022 after we file our annual report on Form 20-F for such fiscal year. However, whether the PCAOB will continue to conduct inspections and investigations completely to its satisfaction of PCAOB-registered public accounting firms headquartered in mainland China and Hong Kong is subject to uncertainty and depends on a number of factors out of our, and our auditor's, control, including positions taken by authorities of the PRC. The PCAOB is expected to continue to demand complete access to inspections and investigations against accounting firms headquartered in mainland China and Hong Kong in the future and states that it has already made plans to resume regular inspections in early 2023 and beyond. The PCAOB is required under the HFCA Act to make its determination on an annual basis with regards to its ability to inspect and investigate completely accounting firms based in the mainland China and Hong Kong. The possibility of being a "Commission-Identified Issuer" and risk of delisting could continue to adversely affect the trading price of our securities. If the PCAOB determines in the future that it no longer has full access to inspect and investigate accounting firms headquartered in mainland China and Hong Kong and we continue to use such accounting firm to conduct audit work, we would be identified as a "Commission-Identified Issuer" under the HFCA Act following the filing of the annual report for the relevant fiscal year, and if we were so identified for two consecutive years, trading in our securities on U.S. markets would be prohibited. For the details of the risks associated with the enactment of the HFCA Act, see "Item 3. Key Information––3.D. Risk Factors––Risks Related to Doing Business in the PRC––Our ADSs may be prohibited from trading in the United States under the HFCAA in the future if the PCAOB is unable to inspect or investigate completely auditors located in China. The delisting of the ADSs, or the threat of them being delisted, may materially and adversely affect the value of your investment."

Cybersecurity Review Measures

On December 28, 2021, the Cyberspace Administration of China, or the CAC, and 12 other relevant PRC government authorities published the amended Cybersecurity Review Measures, or the Cybersecurity Review Measures, which went on February 15, 2022 and supersede and replace the current Cybersecurity Review Measures previously promulgated on April 13, 2020. The Cybersecurity Review Measures provide that the purchase of network products and services by a "critical information infrastructure operator" and the data processing activities of a "network platform operator" that affect or may affect national security shall be subject to the cybersecurity review. Furthermore, if a "network platform operator" that possesses personal information of more than one million users intends to go public in a foreign country, it must apply for a cybersecurity review with the Cybersecurity Review Office. In addition, the relevant PRC governmental authorities may initiate cybersecurity review if they determine certain network products, services, or data processing activities affect or may affect national security.

On November 14, 2021, the CAC released the Regulations for the Administration of Network Data Security (Draft for Comment), or the Draft Data Security Regulations, for public comments. The Draft Data Security Regulations provide that (i) a data processor who processes personal information of more than one million individuals must complete a cybersecurity review if it intends to be listed in a foreign country, and (ii) a data processor who carries out other data processing activities which affect or may affect national security should also complete the cybersecurity review. The Draft Data Security Regulations provide a broad definition of "data processing activities," including collection, storage, usage, processing, transfer, provision, publication, deletion and other activities, which covers the entire life cycle of data processing. The Draft Data Security Regulations also provide a broad definition of "data processors" as individuals and entities that may autonomously determine the purpose and method of data processing activities. In addition, the Draft Data Security Regulations require data processors who process important data or whose securities are listed outside of China to carry out annual data security assessment either by itself or through a third party data security service provider and submit the assessment report to a local agency of the CAC. See "Item 4. Information of the Company—4.B. Business Overview—Regulation—Other PRC Government Regulations— Regulations on Information Security and Data Protection" for detailed discussion. As advised by our PRC legal counsel, Jingtian & Gongcheng, the Draft Data Security Regulations were released for public comment only with the deadline of submitting public comments or opinions by December 13, 2021, and its provisions and anticipated adoption or effective date are subject to changes and thus its interpretation and implementation remain substantially uncertain. We cannot predict the impact of the Draft Data Security Regulations, if any, at this stage, and we will closely monitor and assess any development in the rule-making process.

As advised by our PRC legal counsel, Jingtian & Gongcheng, given the nature of our business, since we do not possess or process personal information of more than one million users/individuals, and we do not believe we are a "critical information infrastructure operator," "network platform operator" or a data processor whose purchase of network products and services or data processing activities affect or may affect national security, the listing of our ADSs on the Nasdaq and future potential offering of our ADSs will not be subject to the cybersecurity review process under the Cybersecurity Review Measures, although we cannot guarantee that the relevant PRC regulatory authority will agree with our interpretation. Currently, the Cybersecurity Review Measures and the Draft Data Security Regulations have not materially affected our business and operations, but in anticipation of the strengthened implementation of cybersecurity laws and regulations and the continued expansion of our business, we face potential risks if we are deemed as a critical information infrastructure operator, a network platform operator or data processing operator under the PRC cybersecurity laws and regulations. In such case, we must fulfill certain obligations as required under the PRC cybersecurity laws and regulations, including, among others, storing personal information and other important data collected and produced within the PRC territory as we advance our drug discovery pipelines as part of our future operations in China, and we may be subject to lengthy cybersecurity review, annual data security assessment and other enhanced regulatory requirements when purchasing network products and services or conducting other data processing activities. We may face challenges in addressing such enhanced regulatory requirements and be required to make necessary changes to our internal policies and practices in data privacy and cybersecurity matters. As advised by our PRC legal counsel, Jingtian & Gongcheng, as of the date of this annual report, no detailed rules or implementation of the Cybersecurity Review Measures have been issued by the CAC and the Draft Data Security Regulations were only released for public comments, and the PRC governmental authorities have broad discretion in the interpretation and enforcement of these laws and regulations. It also remains uncertain whether the future regulatory changes will impose additional restrictions on companies like us. We cannot predict the impact of the Cybersecurity Review Measures and/or the Draft Data Security Regulations, if any, at this stage, and we will closely monitor and assess any development in the rule-making process. If the future enacted laws and regulations, including the enacted version of the data security regulations mandate clearance of cybersecurity review and other specific actions to be completed by companies like us before we are able to complete this offering, we will face uncertainties as to whether such clearance and/or other specific actions can be timely obtained or completed, or at all. If we are not able to comply with the cybersecurity and data privacy requirements in a timely manner, or at all, we may be subject to government enforcement actions and investigations, fines, penalties, or suspension of our non-compliant operations, among other sanctions, which could materially and adversely affect our business and results of operations. Any failure to complete the required cybersecurity review may result in administrative penalties, including fines, a shut-down of our business, revocation of requisite licenses, as well as reputational damage or legal proceedings or actions against us, which may have material adverse effects on our business, financial condition and results of operations. As of the date of this annual report, we have not been involved in any investigation on cybersecurity review made by the CAC on such basis, and we have not received any inquiry, notice, warning, or sanction in such respect, and we have not been subject to any material fines or other material penalties due to non-compliance with cybersecurity or data privacy laws or regulations. Our PRC legal counsel does not expect that, as of the date of this annual report, we are required to file an application for the cybersecurity review by CAC in connection with our previous issuance of securities to foreign investors or maintaining our listing status on Nasdaq. We have been making continuous efforts to comply with the relevant cybersecurity and data protection laws and regulations of the PRC, and will endeavor to comply with any updated applicable laws, regulations or guidelines as issued by any relevant regulatory authority in the PRC. See "Item 3 Key Information—3.D.Risk Factors—Risks Related to Doing Business in the PRC—Failure to comply with existing or future laws and regulations related to privacy or data security could lead to government enforcement actions, which could include civil or criminal fines or penalties, investigation or sanction by regulatory authorities, private litigation, other liabilities, and/or adverse publicity."

Material Licenses and Approvals

Our PRC subsidiary has obtained all material licenses and approvals required for our operations in China. For details of our material licenses and approvals, see "Item 4. Information of the Company—4.B. Business Overview—Material Licenses and Approvals." For risks relating to licenses and approvals required for our operations in China, see "Item 3. Key Information—3.D. Risk Factors—Risks Related to Doing Business in the PRC," "—Risks Related to Clinical Development of Our Product Candidates," and "—Risks Related to Obtaining Regulatory Approval of Our Drug Candidates."

Furthermore, in connection with our historical issuance of securities to foreign investors, under currently effective PRC laws, regulations and regulatory rules, as of the date of this annual report, we are not currently required to obtain permissions from the China Securities Regulatory Commission (the "CSRC"), and we have not received any formal notice from any PRC authority indicating that we should apply for or are otherwise subject to cybersecurity review or security assessment. In addition, we have not been asked to obtain such permissions by any PRC authority or received any denial to do so. However, the PRC government has recently indicated an intent to exert more oversight and control over offerings that are conducted overseas and/or foreign investment in China-based issuers. For example, the CSRC published the Trial Measures and Listing Guidelines on February 17, 2023, designed to regulate overseas securities offerings by PRC domestic companies. Given the recent nature of the introduction of the Trial Measures and Listing Guidelines, there remains significant uncertainty as to the enactment, interpretation and implementation of regulatory requirements related to overseas securities offerings and other capital markets activities.

If (i) we mistakenly conclude that certain regulatory filings, permissions and approvals are not required or (ii) applicable laws, regulations, or interpretations change and (iii) we are required to obtain such filings, permissions or approvals in the future, but fail to receive or maintain such filings, permissions or approvals, we may face sanctions by the CSRC, the Cyberspace Administration of China (the "CAC") or other PRC regulatory agencies. In addition, rules and regulations in China can change quickly with little advance notice. These regulatory agencies may impose fines and penalties on our operations in China, limit our operations in China, limit our ability to pay dividends outside of China, limit our ability to list on stock exchanges outside of China or offer our securities to foreign investors or take other actions that could have a material adverse effect on our business, financial condition, results of operations and prospects, as well as the trading price of our securities. Our non-consolidated joint venture faces the same risks as well. See also "Item 3 Key Information—3.D.Risk Factors—Risks Related to Doing Business in the PRC—We may be required to obtain approval or complete filing or other requirements of the CSRC or other PRC government authorities in connection with our issuances of securities overseas, and, if required, we cannot predict whether we will be able to obtain such approval or complete such governmental procedure."

Transfer of Funds and Other Assets

Under relevant PRC laws and regulations, we are permitted to remit funds to Adagene Suzhou through loans, capital contributions or as payment of considerations for the services rendered. In 2020, 2021 and 2022, Adagene Inc. made payments of US$15.5 million, US$30.0 million and US$24.5 million, respectively, in cash to Adagene Suzhou as consideration for providing services associated with research and development activities related to those intellectual properties owned by Adagene Inc. There were no intercompany loans provided by Adagene Inc. to Adagene Suzhou during the years ended and as of December 31, 2020, 2021 and 2022. In addition, as advised by our PRC legal counsel, Jingtian & Gongcheng, Adagene Suzhou is able to mark up and charge to Adagene Inc., its ultimate parent, for providing services associated with research and development activities related to those intellectual properties owned by Adagene Inc. and Adagene Inc. is able to make cash payments to Adagene Suzhou for considerations of such services. In the future, cash proceeds raised from overseas financing activities, including this offering, may be transferred by Adagene Inc., the Cayman holding company, (i) through Adagene (Hong Kong) Limited, our Hong Kong subsidiary, to Adagene Suzhou, our PRC subsidiary, and (ii) to Adagene Incorporated, our U.S. subsidiary, via capital contribution, shareholder loans or consideration for the services rendered, as the case may be.

Other than the above disclosed transfer of funds, we did not transfer any type of assets between Adagene Suzhou and other Adagene subsidiaries in 2020, 2021 and 2022.

Restrictions on Foreign Exchange and the Ability to Transfer Cash between Entities, Across Borders and to U.S. Investors

If we become profitable, Adagene Inc.'s ability to pay dividends, if any, to the shareholders and ADS investors and to service any debt it may incur will depend upon dividends paid by our PRC and U.S. subsidiaries. Under the PRC laws and regulations, our PRC subsidiary is subject to certain restrictions with respect to paying dividends or otherwise transferring any of their net assets offshore to Adagene Inc. In particular, under the current effective PRC laws and regulations, dividends may be paid only out of distributable profits. Distributable profits are the net profit as determined under PRC GAAP, less any recovery of accumulated losses and appropriations to statutory and other reserves required to be made. Our PRC subsidiary shall appropriate 10% of the net profits as reported in its respective statutory financial statements (after offsetting any prior year's losses) to the statutory surplus reserves until such reserves have reached 50% of its respective registered capital. In addition, the EIT Law and its implementation rules provide that a withholding tax rate of up to 10% will be applicable to dividends payable by Chinese companies to non-PRC-resident enterprises unless otherwise exempted or reduced according to treaties or arrangements between the PRC central government and governments of other countries or regions where the non-PRC-resident enterprises are incorporated. See "Item 3.D.Risk Factors—Risks Related to Doing Business in the PRC—We may rely on dividends and other distributions on equity paid by our PRC subsidiary to fund any cash and financing requirements we may have, and any limitation on the ability of our PRC subsidiary to make payments to us could have a material and adverse effect on our ability to conduct our business." Further, if any of our subsidiaries incurs debt on its own behalf in the future, the instruments governing such debt may also restrict its ability to pay dividends ultimately to Adagene Inc. As a result, our PRC subsidiary may not have sufficient, or any, distributable profits to pay dividends to us in the near future.

Furthermore, if certain procedural requirements are satisfied, the payment of current account items, including profit distributions and trade and service related foreign exchange transactions, can be made in foreign currencies without prior approval from State Administration of Foreign Exchange ("SAFE") or its local branches. However, where RMB is to be converted into foreign currency and remitted out of China to pay capital expenses, such as the repayment of loans denominated in foreign currencies, approval from or registration with competent government authorities or its authorized banks is required. The PRC government may take measures at its discretion from time to time to restrict access to foreign currencies for current account or capital account transactions. If the foreign exchange control system prevents us from obtaining sufficient foreign currencies to satisfy our foreign currency demands, we may not be able to pay dividends in foreign currencies to our offshore intermediary holding companies or ultimate parent company, and therefore, our shareholders or investors in our ADSs. Further, we cannot assure you that new regulations or policies will not be promulgated in the future, which may further restrict the remittance of RMB into or out of the PRC. We cannot assure you, in light of the restrictions in place, or any amendment to be made from time to time, that our current or future PRC subsidiaries will be able to satisfy their respective payment obligations that are denominated in foreign currencies, including the remittance of dividends outside of the PRC. See "Item 4 Information on the Company—PRC Regulation —Regulations on Foreign Exchange and Dividend Distribution" for detailed discussion.

For PRC and United States federal income tax consideration of an investment in the ADSs, see "Item 10. Additional Information—10.E. Taxation."

4.B. Business Overview

OVERVIEW

We are a platform-driven, clinical-stage biotechnology company transforming the discovery and development of novel antibody-based cancer immunotherapies. We are combining computational biology and artificial intelligence to design novel antibodies that address unmet patient needs. Powered by our proprietary Dynamic Precision Library (DPL) platform, which fuels our NEObody™, SAFEbody®, and POWERbody™ technologies, we are developing a highly differentiated pipeline of novel immunotherapies. We have forged strategic collaborations with reputable global partners that leverage our technology in multiple approaches at the vanguard of science.

We aim to push the boundaries of antibody discovery and engineering through the precise design, construction, and selection of antibody product candidates intractable to traditional antibody technology. We have pioneered a dynamic antibody technology interface to harness the conformational diversity of antibodies, which enlarges epitope sampling of a given drug target for differentiated therapeutic antibody development. Additionally, we have a proprietary precision masking technology and specialized antibody engineering capabilities which enable us to design therapeutics with unique features.

Our Dynamic Precision Library (DPL) fuels our three antibody technology platforms, which can be used alone or together to create novel, differentiated antibody-based therapeutic candidates:

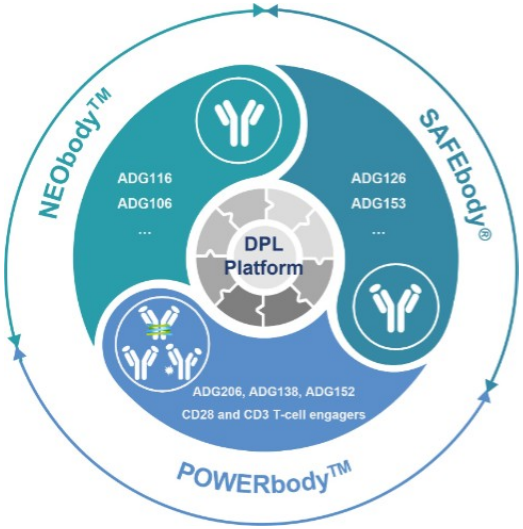
- The NEObody technology platform is a fully synthetic phage display and yeast display-based antibody discovery technology, which we believe is differentiated from other synthetic antibody technologies through its innovative designs and precise constructions. NEObody technology enables the generation of antibodies designed with dynamic binding sites that adapt kinetically to unique epitopes, triggering a novel MOA. The species cross-reactive antibodies generated by NEObody technology not only have the potential to reveal new biological functions of the targets, but also facilitate preclinical studies using various immune system intact animal models, resulting in high fidelity translation from preclinical to clinical studies. We refer to antibodies generated by our NEObody technology as NEObodies.

- The SAFEbody technology platform is designed to mask an antibody binding interface with a masking motif, which then prevents an antibody from binding to its target in healthy tissues, minimizing on target, off tumor toxicities. The masking motif is designed to activate, or unmask, the antibody to allow binding in the tumor microenvironment, or TME, where certain activation conditions such as a protease is upregulated as compared to healthy tissues, allowing the antibody to bind to its target for tumor killing. Our SAFEbody enabled therapeutic candidates are therefore designed to be activated predominantly in the TME while remaining largely in an inactive state in healthy tissues. Our SAFEbody technology can be applied to mask the binding sites of any antibodies including but not limited to NEObodies. We refer to such masked antibodies as SAFEbodies. Notably, SAFEbody technology can be applied to our NEObodies, such as what we did with ADG116 to potentially achieve an increased therapeutic index with ADG126.

- The POWERbody technology platform enables the creation of new versions of antibodies, which may be bispecific T-cell engagers, or TCEs, or Fc-engineered antibodies, antibody-drug conjugates, or ADCs, or antibodies that are designed to reach beyond the therapeutic potency of traditional monospecific antibodies. Our POWERbody candidates incorporate SAFEbody precision masking technology and are designed to improve antitumor activity while maintaining the enhanced safety profile. As an example, we have developed bispecific TCEs with either a CD3 or a CD28 arm and demonstrated the ability to combine them together for potentially safe and durable immunotherapies.

Our AI-powered technology allows us to engineer and select species cross-reactive antibodies designed to dynamically adapt to unique and evolutionally conserved epitopes. We believe that comprehensive *in vivo* preclinical evaluations using these species cross-reactive antibodies are the key to assess the efficacy and safety potential of tailor-made antibody candidates before progressing them into lengthy and costly clinical trials. Our NEObody, SAFEbody and POWERbody technology platforms are all designed to facilitate favorable druggability, manageable CMC attributes, and reduced immunogenicity.

The figure below shows how our NEObody, SAFEbody, and POWERbody technologies are inter-connected with our DPL and utilized for the building of our product pipeline of mono- and combination immunotherapies.



Our DPL Platform fuels three antibody technology platforms, which can be used alone or together to create novel, differentiated antibody-based therapeutic candidates. Antibodies generated by NEObody technology are designed with dynamic binding sites that adapt kinetically to unique epitopes, thereby triggering a novel MOA. SAFEbody technology is designed to address safety and tolerability challenges associated with many antibody therapeutics by using precision masking technology to shield the binding domain of the biologic therapy. Through activation in the TME, this allows for tumor-specific targeting of antibodies, while minimizing on-target off-tumor toxicity in healthy tissues. POWERbody candidates are designed to unleash the efficacy of a therapeutic through Fc-engineering, drug conjugation, or T-cell engagement, while securing safety by precision masking with SAFEbody technology. Thus, POWERbody candidates also incorporate SAFEbody precision masking technology.

Our Robust, Transformative Pipeline

By leveraging our proprietary DPL platform and three platform technologies, we have developed a robust pipeline of innovative product candidates in various stages of development, ranging from research and discovery to preclinical and clinical development. Our highly differentiated and wholly-owned clinical-stage pipeline consists of two anti-CTLA-4 antibodies, ADG116 (NEObody) and ADG126 (SAFEbody), which are both in Phase 1b/2 clinical evaluation in single agent and/or combination clinical trials designed to evaluate safety and preliminary efficacy, and two anti-CD137 antibodies, ADG106 (NEObody) and ADG206 (POWERbody). We also have several programs in IND-enabling studies, including an IND-ready masked, IgG1 anti-CD47 SAFEbody.

In addition, we have out-licensed the Greater China rights of ADG104, an anti-PD-L1 mAb currently in Phase 2 clinical development, to Sanjin, and the Greater China rights of ADG125, a novel anti-CSF-1R mAb in Phase 1 development, to Dragon Boat Biopharmaceuticals. We have the right to apply for the patents derived from our core and key technologies pertaining to ADG104 and ADG125 in the rest of the world, where we retain a majority of the economic benefits.

The following chart provides an overview of the status of each of our wholly-owned clinical and pre-clinical programs for which we have global rights:

A Robust, Transformative Pipeline of Wholly-Owned Assets

We have deployed our NEObody and SAFEbody technology platforms to develop our wholly-owned clinical candidates, ADG116, ADG126, ADG106 and ADG206, which are in ongoing clinical evaluation:

- ADG116 is a fully human anti-CTLA-4 NEObody, which binds to a novel epitope of CTLA-4 different from ipilimumab, the only CTLA-4 mAb approved globally in both monotherapy and in combination with anti-PD-1. The dynamic interface of ADG116 enables not only its species cross-reactivity with human, cynomolgus monkey, and mouse CTLA-4 for preclinical studies, but also its dynamic engagement on a unique epitope of CTLA-4 to trigger a novel MOA distinct from ipilimumab by partial ligand blocking and stronger regulatory T-cell depletion via strong antibody-dependent cellular cytotoxicity (ADCC). ADG116 is designed to overcome the safety challenges of existing CTLA-4 therapeutics, with enhanced Treg depletion, and improved safety and efficacy profiles, with confirmed clinical responses both as monotherapy and in combination with anti-PD-1. ADG116 is currently in phase 1b/2 evaluation.

- ADG126 is a fully human anti-CTLA-4 SAFEbody, which applies SAFEbody precision masking technology to ADG116 to further enhance safety and efficacy profiles by masking the antibody binding site which is then conditionally activated in the TME to limit on target, off tumor toxicity. ADG126 is designed to further increase the therapeutic window of ADG116, and optimize efficacy by achieving higher doses and constant target engagement with repeat dosing of anti-CTLA-4 that may unlock the full potential of CTLA-4 as a proven target for strong ADCC-mediated Treg depletion in the TME. ADG126 has consistently shown best-in-class safety and differentiated efficacy profiles in clinic, which is consistent with and enabled by the broad species cross-reactivity of ADG126 for extensive preclinical evaluation from mouse, rats and monkeys, including GLP toxicology data. In clinic, no dose-limiting toxicities have been observed up to 20 mg/kg. ADG126 is currently in phase 1b/2 evaluation.

- ADG106 is a fully human ligand-blocking agonistic anti-CD137 NEObody, which targets a unique epitope of CD137 that is different from other anti-CD137 antibodies currently under clinical development. Preclinical and clinical studies show that ADG106 is capable of binding to CD137 in a fashion similar to its natural ligand, CD137L. ADG106 is designed to balance safety and efficacy to overcome the known safety challenges of anti-CD137 targeted therapy, particularly when used in combination with anti-PD-1 or anti-CTLA-4 therapies. In clinic, ADG106 has shown a well-tolerated safety profile and evidence of single-agent efficacy, while combination therapy development is supported by the combined findings of our phase 1 monotherapy trials, data from extensive preclinical studies, as well as PD marker-based modelling from prior and ongoing trials. Phase 1b/2 investigator-initiated trials in combination settings are ongoing.

- ADG206 is a masked, Fc engineered anti-CD137 agonistic POWERbody. ADG206 incorporates SAFEbody® precision masking technology and is designed to achieve improved safety and efficacy. ADG206 has demonstrated enhanced crosslinking by FcgRIIb in vitro upon activation and antitumor activity in vivo, while the SAFEbody masking technology limits on-target off-tumor toxicities by preferential activation in the TME. ADG206 is currently in Phase 1 evaluation.

Additionally, we have multiple preclinical programs that are currently in IND-enabling studies as candidates for future clinical development as resources allow. See "*—IND-ready Candidates and Preclinical Pipeline*".

Our Global Partnerships and Collaborations

We have a successful track record of collaborations and partnerships with global biopharmaceutical companies and academic institutions. So far, we have established multiple collaborations and we continue to seek partnership opportunities where we can leverage our proprietary technology platform to develop novel antibodies to address unmet medical needs.

We enter into collaborations with biotechnology and pharmaceutical companies to leverage the power of our technology platforms, creating a network of potential future revenue streams that complement future long-term value from our wholly-owned pipeline. These collaborations include both technology licensing agreements and outlicensing of product candidates, both of which allow us to retain significant future participation in product sales through royalties paid on net sales. In the future, we may also enter into strategic collaborations which may involve joint development for our preclinical and/or clinical assets to both accelerate the path to clinic and drive global commercialization.

We have entered into technology licensing agreements with Sanofi, Exelixis and ADC Therapeutics to develop antibody-based therapeutics against tumor targets using our SAFEbody technology. We have also out-licensed the Greater China rights for two antibody candidates to Sanjin and its affiliates. Additionally, we have leveraged our DPL technology platform and antibody discovery and engineering capabilities in discovery collaborations with the U.S. National Institutes of Health (NIH), Mitsubishi Tanabe, Celgene (now BMS), GSK and Hengrui. To further advance our pipeline, we have also put in place various clinical collaborations, including an agreement with Roche who is sponsoring and conducting a randomized combination trial with ADG126, clinical collaborations and supply agreements with Merck who will provide pembrolizumab for certain of our combination clinical trials, and an agreement with research organizations in Singapore for investigator-initiated trials of our ADG106 clinical candidate in combination settings. See "*—Clinical Collaboration Agreements*".

Our collaborations empower our growth by generating cash flow and revenues that partially offset expenditures on our internal research and development programs, expand our knowledge base regarding antibody technology across multiple targets and antibodies provided by our partners, and provide us with future joint development opportunities.

OUR CLINICAL PIPELINE

By leveraging our proprietary DPL platform and three platform technologies, we have developed a robust pipeline of innovative product candidates in various stages of development, ranging from research and discovery to preclinical and clinical development.

Our wholly owned, highly differentiated pipeline consists of two anti-CTLA-4 clinical candidates, ADG116 NEObody, ADG126 SAFEbody (with masking), and two anti-CD137 candidates, ADG106 NEObody and ADG206 POWERbody (with masking). We also have multiple IND-ready preclinical candidates and a discovery pipeline in various stages of development.

In addition, we have out-licensed the Greater China rights of ADG104, an anti-PD-L1 mAb in Phase 2 development, to our partner Sanjin, and the Greater China rights of ADG125, a novel anti-CSF-1R mAb in Phase 1 development, to Dragon Boat Biopharmaceuticals. We have the right to apply for the patents derived from our core and key technologies pertaining to ADG104 and ADG125 in the rest of the world, where we retain a majority of the economic benefit.

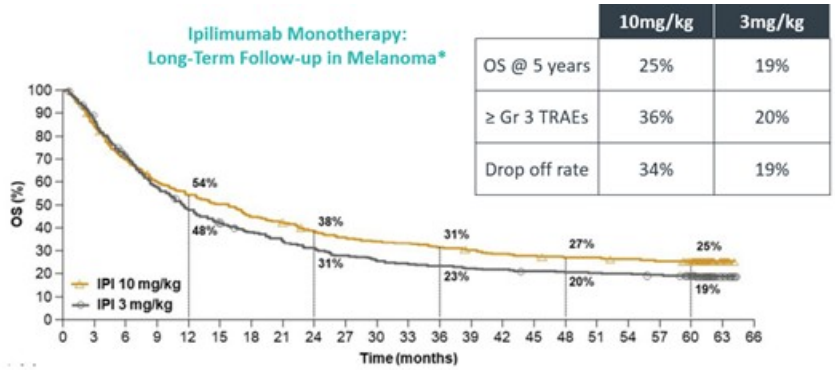
Together, our wholly-owned internal candidates and partnered programs provide multiple product development and future commercial opportunities, either alone or with partners.

About Cytotoxic T-lymphocyte Antigen 4 (CTLA-4) Therapy

The development of immune checkpoint inhibitors has revolutionized cancer immunotherapy in the past decade. In fact, recent trials have shown that immunotherapy can induce durable and extensive tumor regression, potentially converting previously fatal diseases into chronic, manageable diseases for certain patients.

Anti-CTLA-4 therapy is one of the first immune checkpoint inhibitor treatments to demonstrate definite clinical benefit through direct T-cell activation. Ipilimumab (Yervoy®) was the first approved immune checkpoint inhibitor by the FDA in 2011 for the treatment of advanced melanoma. This was followed by FDA approval in 2022 of tremelimumab (Imjudo®) in combination with anti-PD-L1 for treatment of unresectable hepatocellular carcinoma (HCC) and metastatic non-small cell lung cancer (NSCLC) after more than ten years, while more than ten anti-PD-1/PD-L1 therapies and their combinations were approved globally with comparable safety and efficacy profiles, highlighting the unique challenge to unleashing the full therapeutic potential for anti-CTLA-4 therapies. Indeed, anti-CTLA-4 therapies approved or in clinical development show a strong dose- dependent toxicity and efficacy, both alone and in combination with anti-PD-1/L1, limiting their acceptance in clinical practice.

The following chart demonstrates the dose-dependent toxicities with ipilimumab monotherapy treatment in melanoma, limiting its dosing and therefore efficacy:



* Reference: Ascierto PA, et al. J Immunother Cancer 2020;8:e000391. doi:10.1136/jitc-2019-000391

The following chart shows that ipilimumab has a strong dose-dependent toxicity and efficacy in the combination setting with anti-PD-1, as shown for second-line HCC:

Ipilimumab: Combination Data in HCC Highlight Dose Dependent Challenge of Anti-CTLA-4 Therapy

Tumor Type	Ipilimumab Dosing Regimens	Overall Survival (OS)	TRAE >=G3	AEs Lead to Discontinuation	Trial
HCC	1 mpk @ q3w	12 months	29%	6%	NCT01658878
HCC	3 mpk @ q3w	23 months	53%	18%	NCT01658878
Ratio	3 x	~2 x	~2 x	3 x	

For HCC, approved dose level is Nivo 1mg/kg+ Ipi 3mg/kg; Nivo + 4 doses of Ipi; patient population is previously treated with sorafenib (2L); dosing regimens Q3W for 4 doses.

Indeed, ipilimumab is still being debated for its function in blocking CTLA-4 via its binding arms or in depleting CTLA-4 expressing Treg cells intratumorally for anti-CTLA-4 therapies. Thus, development of next generation anti-CTLA-4 therapies with an improved safety profile and antitumor efficacy through enhanced CTLA-4 blockage and/or Treg depletion (via its Fc-mediated ADCC effect) are urgently needed to improve upon existing anti-CTLA-4 therapies, as well as open the new doors to treat cold tumors such as MSS-CRC. Additionally, addressing the dose-dependent toxicities of anti-CTLA-4 therapy may enable more front-line combinations, fully unlocking the potential of anti-CTLA-4 as a cornerstone of cancer care.

ADG116 NEObody: A Unique Entry Point for Anti-CTLA-4 Therapy

ADG116 is a fully human anti-CTLA-4 antibody generated using our NEObody technology, designed to target a unique epitope of CTLA-4, to enhance the efficacy profile and to address both the toxicity and efficacy concerns associated with existing CTLA-4 therapeutics. It is currently under Phase 1b/2 clinical evaluation in multiple trials in the U.S., China and Asia Pacific (APAC), both as monotherapy and in combination with other therapies.

The development rationale for ADG116 focuses on its softer CTLA-4 ligand blocking and stronger ADCC for depleting regulatory T-cells than ipilimumab. In a head-to-head *in vivo* efficacy study, ADG116 was observed to have a five-fold greater anti-tumor activity in comparison with ipilimumab. In addition, ADG116 was observed to induce antitumor responses concomitant with reduced immunosuppressive regulatory T-cell and enhanced cytotoxic T lymphocyte ($CD8^+$ T-cells) activities in the TME.

Our clinical program is designed to demonstrate the differentiated safety and efficacy profile of ADG116 and to support our evaluation of our anti-CTLA-4 SAFEbody ADG126, for which ADG116 is the parental antibody.

We initiated a monotherapy trial of ADG116 in Australia (ADG116-1003) designed to evaluate safety and determine a recommended Phase 2 dose, or RP2D, in patients with advance metastatic tumors. A secondary objective of the trial is to evaluate preliminary efficacy based upon anti-tumor activity both as monotherapy and in combination regimens. Since 2021, we have expanded the trial (ADG116- 1003) to sites in the U.S. after receiving clearance from the FDA. Upon the receipt of such clearance from the FDA, we terminated a prior Phase 1 trial (ADG116-1001) in the U.S. for business reasons. In addition, we obtained approval to initiate cohorts in other countries, including Singapore and South Korea. For detailed discussion on our terminated ADG116-1001 clinical trial in U.S., see “Item 3 Key Information—Risk Factors—Risks relating to obtaining regulatory approval of our drug candidates—Our product candidates may cause undesirable adverse events, side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following any regulatory approval.”

In 2022, we completed dose escalation of ADG116 monotherapy up to 15 mg/kg with repeat dosing and initiated dose escalation in combination with anti-PD-1 under the same protocol. In November 2021, we also received clearance from the FDA to initiate a trial of ADG116 in combination with pembrolizumab (ADG116-P001 / KEYNOTE-C97). Data from both of these phase 1b/2 studies were presented in November 2022 at the annual meeting of the Society for Immunotherapy of Cancer (SITC).

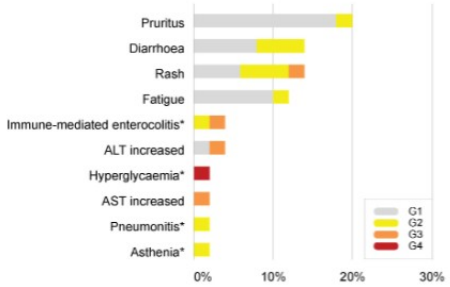
Summary of Clinical Studies & Results

In November 2022, we reported comprehensive safety and interim efficacy data from our ongoing phase 1b/2 monotherapy and combination clinical studies of ADG116 in two poster presentations at SITC 2022.

Results from monotherapy evaluation in patients with advanced/metastatic solid tumors (N=50) showed ADG116 is well tolerated across dose levels with repeat dosing. Grade 1/2 and Grade 3/4 treatment-related adverse events (TRAEs) were reported in 28 (56%) and 3 (6%) patients, respectively. With repeat dosing and tracking for late-onset toxicities in the same 10mg/kg cohort, the overall rate of Grade 3 or higher TRAEs was 13%. There were no Grade 3 or higher TRAEs reported at the 15 mg/kg dose level for ADG116 monotherapy. For reference, the reported rate of TRAEs Grade 3 and higher for the currently approved anti-CTLA-4 therapy, ipilimumab, is approximately 36% at 10 mg/kg in first-line monotherapy in melanoma patients (*Ascierto PA, et al. J Immunother Cancer 2020;8:e000391. Doi:10.1136/jitc-2019-000391*).

The following chart demonstrates the incidence of treatment emergent adverse events with ADG116 by grade and dose level, showing the vast majority of TRAEs were Grade 1 or 2:

ADG116 Monotherapy: TRAEs Show Compelling Safety Profile up to 15 mg/kg with Repeat Dosing*



Dose levels (mg/kg)	N	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G5 n (%)
All	50	31 (62)	17 (34)	11 (22)	2 (4)	1 (2)	0
≤ 0.3	11	3 (27)	3 (27)	0	0	0	0
1	3	2 (67)	2 (67)	0	0	0	0
3	4	3 (75)	1 (25)	2 (50)	0	0	0
6	6	5 (83)	3 (50)	2 (33)	0	0	0
10	23	15 (65)	8 (35)	4 (17)	2 (9)	1 (4)	0
15	3	3 (100)	0	3 (100)	0	0	0

* Results as of the 2022 SITC Data Cut-off Date

At SITC 2022, we also reported preliminary efficacy data from the ongoing monotherapy trial in these heavily pre-treated patients with difficult-to-treat tumors. The overall disease control rate (DCR) was 33% across all monotherapy dose levels, with additional tumor reduction observed in patients with both warm and cold tumors.

Among 36 efficacy evaluable patients as of the SITC data cut-off date, an initial partial response was observed after two cycles of treatment in a Kaposi's sarcoma patient, who was one of three treated with ADG116 monotherapy at 15 mg/kg. An additional partial response was observed as of November 2, 2022 in a patient with renal cell carcinoma who progressed after two prior lines of therapy, including an anti-PD-L1 inhibitor. The patient received four cycles of ADG116 monotherapy at 10 mg/kg with no Grade 3 or higher TRAEs reported.

Further, in February 2023, a third partial response with monotherapy was reported in a patient with MSI-H endometrial cancer. The patient had received five cycles of ADG116 at 10 mg/kg with only Grade 1 TRAEs reported.

In addition to monotherapy evaluation in the ADG116-1003 trial, we received NMPA approval to initiate another monotherapy trial, ADG116-1002 in China, to provide additional clinical data regarding safety and activity of ADG116 in Chinese patients, including the combination of ADG116 and other immunotherapies. Data from the trial are expected to enable China to join our global clinical program. As of this annual report, dose escalation cohorts in the trial are ongoing.

In parallel to the ongoing monotherapy evaluation, we initiated dose escalation cohorts for ADG116 in combination with two anti-PD-1 therapies in the ADG116-1003 (toripalimab) and ADG116-P001 (pembrolizumab) trials. At SITC 2022, we provided an interim update on these trials, which demonstrated the manageable safety profile and early efficacy in 15 heavily pre-treated patients with difficult-to-treat tumors.

ADG116 was dosed every three weeks at 3 mg/kg or 6 mg/kg in combination with 240 mg of toripalimab (N=9). Although ADG116 with toripalimab at 6 mg/kg did not meet the target toxicity level (TTL) (i.e., lower rate of Grade 3 or higher TRAEs than those approved for anti-CTLA-4 and anti-PD-1 combination therapies), 3 mg/kg of ADG116 every three weeks with toripalimab was both manageable within the TTL and demonstrated impressive efficacy profile in difficult-to-treat tumors. Further dose optimization is planned, including ongoing evaluation of late-onset toxicities associated with ADG116 plus toripalimab with repeat dosing to meet the desired TTL.

Among seven efficacy evaluable patients who received ADG116 in combination with toripalimab, one confirmed complete response was observed in a patient with platinum-refractory recurrent head and neck squamous cell carcinoma (HNSCC). The patient received 3 mg/kg of ADG116 in combination (n=5; Objective response rate = 20%; DCR = 100%). Lesions completely disappeared after two cycles of therapy, and the durable response was maintained far beyond six cycles as of the SITC Data Cut-off Date. The patient remains on therapy.

A second combination trial, ADG116-P001, evaluated ADG116 in combination with pembrolizumab in pre-treated patients (N=6) primarily with cold tumors. The findings were presented at SITC and further support the differentiated safety profile of ADG116 dosed at 3 mg/kg every three weeks, as well as its efficacy potential when combined with pembrolizumab at a flat dose of 200 mg. No TRAEs higher than Grade 3 were reported and no DLT was observed.

In the combination trial with pembrolizumab, significant changes were observed in a tumor-related biomarker in two patients with metastatic microsatellite-stable (MSS) colorectal cancer (CRC), who experienced a 43% and 27% reduction in carcinoembryonic antigen (CEA) levels, respectively. Both patients had either liver or lung metastases. These data support continued evaluation of ADG116 plus pembrolizumab as a combination of anti-CTLA-4 and anti-PD-1 therapies that may improve outcomes in certain patients with difficult-to-treat tumor types such as MSS-CRC observed here.

Clinical Development Plan

Our clinical development of ADG116 is focused on expanding its safety and efficacy profiles in combination with anti-PD-1 therapy. Combination dose expansion cohorts for ADG116 with anti-PD-1 therapy are ongoing for dose optimization.

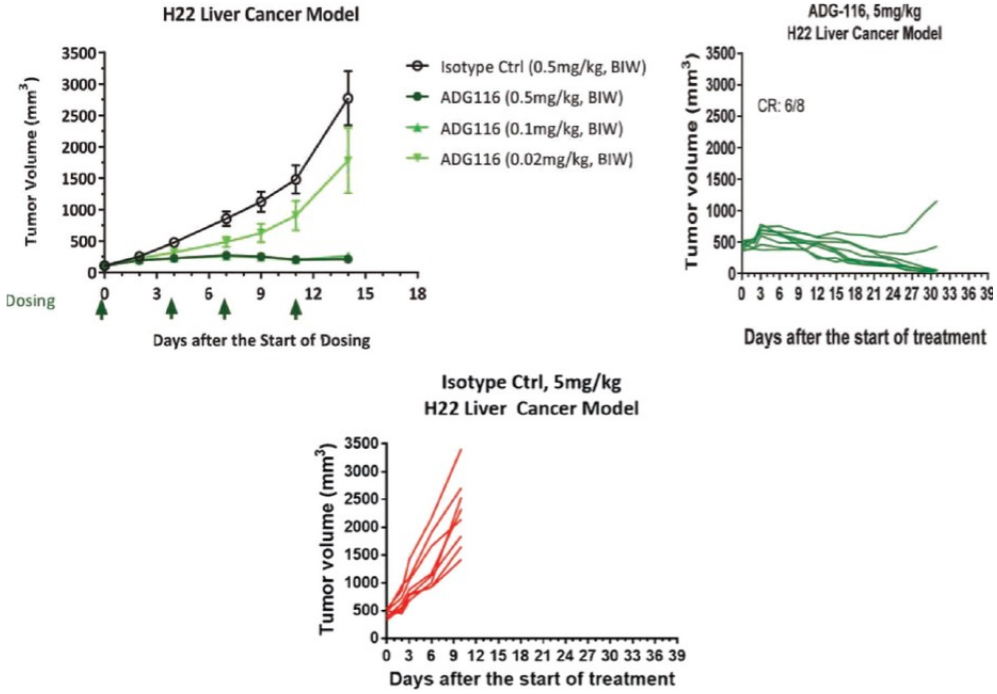
ADG116 Background: Mechanism of Action & Preclinical Profile

We have previously conducted extensive preclinical analysis and modeling to establish the safety and efficacy potentials of ADG116, which is also the parental antibody for our masked, anti-CTLA-4 SAFEbody candidate, ADG126. We have persistently and pursued and implements seamless translational studies using the epitope across different species for both programs, observing a good correlation between preclinical and clinical results both as single agents and in combination with anti-PD-1. Taken together, these preclinical studies (summarized below) have demonstrated that ADG116 has at least a five-fold greater potency profile than ipilimumab, a commercially-available anti-CTLA-4 therapy, and superior activity in various tumor specific models, while its safety profile is at least three-fold better based on GLP monkey data.

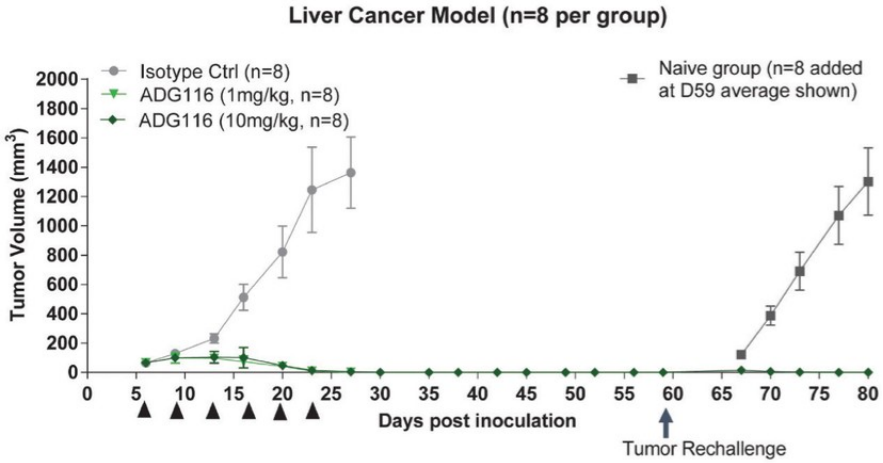
ADG116 is designed to target a unique conserved epitope of CTLA-4. In preclinical studies, ADG116 was observed to have partial CTLA-4 ligand blocking and stronger ADCC for regulatory T-cell depletion than ipilimumab, even with the same Fc isotype. ADG116 has been observed in preclinical animal studies to mediate effector functions to eliminate CTLA-4 highly expressed cells, particularly regulatory T-cells in TME through strong ADCC effect. These actions of ADG116 could lead to enhanced activation and proliferation of tumor infiltrating T-effector cells and reduced T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including an enhanced antitumor immune response.

We extensively evaluated ADG116 in both *in vitro* and *in vivo* preclinical studies. Our *in vivo* efficacy studies were conducted in mice, and safety evaluations were conducted in both cynomolgus monkeys and rats. ADG116 was observed to show robust *in vivo* anti-tumor activity in multiple syngeneic mouse tumor models. Ipilimumab was included as a benchmark and was compared with ADG116 in a series of our preclinical studies. In these preclinical studies, we observed that ADG116 had a potential advantage over ipilimumab in potentiating T-cell activation. While ADG116 has partial CTLA-4 ligand blocking, it was observed to have superior ability in eliminating CTLA-4 positive regulatory T-cells via ADCC in tumors resulting in enhanced antitumor responses. ADG116 was well tolerated in rats and cynomolgus monkeys at doses up to 30 mg/kg in GLP-compliant four-week repeat-dose toxicology studies

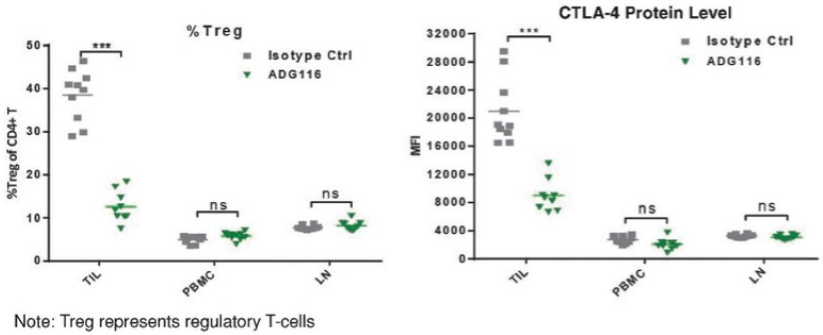
Preclinical Pharmacology: We evaluated ADG116 as a monotherapy *in vivo* in an H22 liver cancer syngeneic mouse model. As shown in the figure below, ADG116 was observed to induce an encouraging antitumor response at low doses in a dose-dependent manner (see figure below on the left). Additionally, ADG116 was observed to inhibit tumor growth of large tumors in the same model (see figure below on the right).



As illustrated in the below figure, in a liver cancer tumor rechallenge study, ADG116 was observed to induce significant antitumor response. Fifty-nine days after the initial tumor inoculation and more than 30 days after the last ADG116 treatment, mice were then rechallenged with the same tumor. We observed that mice that responded to the initial ADG116 treatment remained tumor-free even without additional ADG116 treatment while naïve mice developed tumors, indicating the development of antitumor memory response elicited by ADG116.



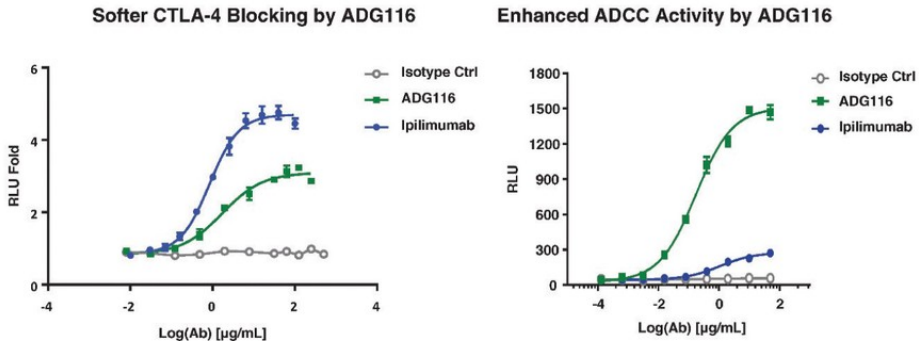
Since ADG116 was observed to exhibit strong ADCC activity *in vitro*, we evaluated the ability of ADG116 to deplete regulatory T-cells *in vivo* in a CT26 mouse colon cancer syngeneic model. ADG116 treatment was observed to specifically deplete regulatory T-cells in the tumor, but not in peripheral blood mononuclear cells, or PBMCs, or lymph nodes. The following figure shows significant regulatory T-cell depletion (left figure) and inhibition of CTLA-4 expression (right figure) in tumors by ADG116.



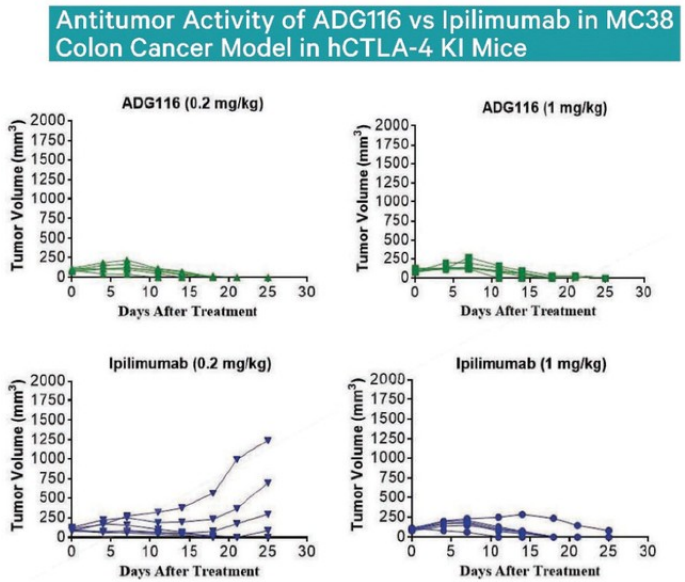
Note: Treg represents regulatory T-cells

In a series of preclinical studies, we compared the effect of ADG116 to ipilimumab. We believe that these studies suggest that ADG116 has a unique MOA compared to ipilimumab and has a potential advantage over ipilimumab in eliciting antitumor responses. These preclinical trial results support the further clinical evaluation of ADG116 as a monotherapy and in combination with other therapies for a wide range of tumor types.

In the CTLA-4 blockade bioassay illustrated in the figure below on the left, ADG116 was observed to exhibit weaker blocking than ipilimumab of CTLA-4's ability to inhibit CD80- and CD86-induced IL-2 production. This result supports our belief that ADG116 can function as a CTLA-4 checkpoint inhibitor with weaker activity than ipilimumab, which may result in less systemic autoimmune side effects on normal tissues. On the other hand, ADG116 was observed to exhibit notably stronger ADCC activity than ipilimumab in the *in vitro* assay shown in the figure below on the right. Since CTLA-4 is expressed on regulatory T-cells, we believe that ADG116 offers a potential advantage over ipilimumab in depleting regulatory T-cells by means of ADCC. We subsequently investigated this *in vivo* in a syngeneic mouse tumor model.



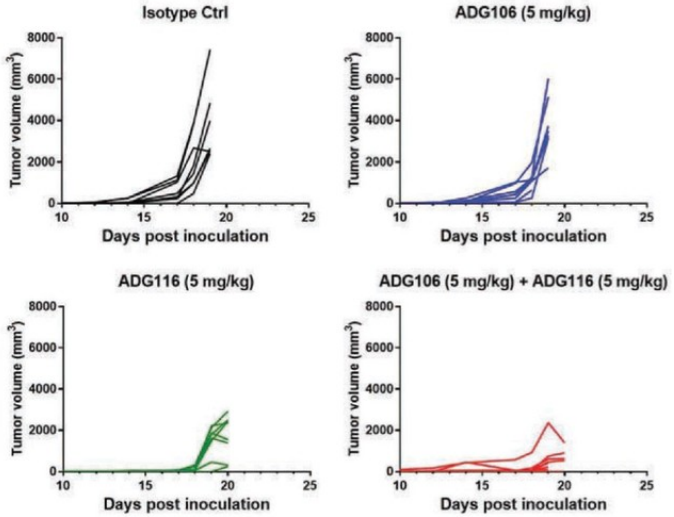
To compare ADG116's *in vivo* antitumor activity to ipilimumab, we utilized a subcutaneous MC38 mouse syngeneic colon cancer model in hCTLA-4, knock-in, or KI, C57BL/6 mice. We selected the hCTLA-4 KI mice as ipilimumab does not cross-react with mouse CTLA-4. As shown in the figure below, ADG116 was observed in this study to exhibit stronger antitumor activity than ipilimumab (ADG116 at 0.2 mg/kg induced equivalent antitumor response as 1 mg/kg of ipilimumab).



As shown in the figure below, we measured tumor infiltrating regulatory T-cells in the subcutaneous hCTLA-4 KI MC38 mouse colon cancer model after ADG116 or ipilimumab treatment. Among the TILs, the percentage of regulatory T-cells was observed to be significantly reduced after ADG116 treatment while the regulatory T-cell reduction after ipilimumab treatment was not significant. Notably, we observed that regulatory T-cell depletion by ADG116 occurred only in the TME, and not in PBMCs or the spleen. We believe that these results provide a mechanistic rationale for the enhanced *in vivo* antitumor activity of ADG116 compared to ipilimumab. ADG116 may reduce the immunosuppressive regulatory T-cell activity specifically in the TME to enhance antitumor immune responses.

As illustrated below, in addition to evaluating the efficacy of ADG116 as a monotherapy, we also evaluated ADG116 in combination therapies. ADG116 was observed to have an antitumor effect with an anti-PD-1 treatment in a Lewis lung cancer syngeneic mouse model.

We also examined the effects of ADG116 in combination with our CD137 agonistic antibody, ADG106, in a B16F10 melanoma syngeneic mouse model. As shown below, we observed that the combination of ADG116 with ADG106 enhanced the antitumor activity compared with ADG116 or ADG106 alone.



Preclinical Toxicology: We performed preclinical toxicology studies in cynomolgus monkeys and rats to evaluate the toxicity of ADG116. There were no abnormal findings in the single-dose toxicology studies. We observed that ADG116 was well tolerated in both cynomolgus monkeys and rats at up to 200 mg/kg. In a GLP-compliant, four-week repeat-dose toxicology study, ADG116 was tolerated at doses up to 30 mg/kg/dose (five doses per week). In this study, ADG116 related hematology parameter changes, serum chemistry changes, mononuclear infiltration of predominantly lymphocytes with fewer macrophages into the parenchyma of numerous organs were the primary test article-related effects evaluated. These changes were reversible at ≤ 30 mg/kg/dose, and consistent with the biological role of CTLA-4 in regulating and maintaining peripheral immune tolerance. The NOAEL was considered to be 30 mg/kg/dose in both rats and cynomolgus monkeys.

ADG126 SAFEbody: A Best-in-Class Anti-CTLA-4 Therapy

Our most advanced SAFEbody program, ADG126, is a masked fully-human anti-CTLA-4 mAb engineered to address the safety concerns associated with existing CTLA-4 therapeutics, while maintaining potency when locally activated in the TME. It is currently under Phase 1b/2 clinical evaluation in multiple trials in the U.S., China and APAC, both as monotherapy and in combination with anti-PD-1 therapy.

ADG126 is designed to address the toxicity issues of the approved CTLA-4 immuno-oncology therapy and achieve enhance anti-tumor efficacy to expand the potential of CTLA-4 as a target for the treatment of cancer. It applies our proprietary SAFEbody technology to a parental antibody, ADG116, enabling ADG126 to be activated primarily in tumor tissues rather than healthy tissues, minimizing the risk of on-target, off-tumor toxicities.

In September 2022, we presented the first clinical results from our monotherapy evaluation in a poster presentation at the European Society of Medical Oncology (ESMO) annual congress. The data showed a best-in-class safety profile for ADG126 with repeat dosing and anti-tumor activity observed in cold tumors with steady accumulation of activated ADG126. During 2022, we also continued to advance global dose escalation trials of ADG126 in combination with anti-PD-1 therapies. In January 2023, we announced interim findings from these trials showing the combination safety profile and confirmed clinical responses with ADG126 up to 10 mg/kg with repeat cycles in combination with anti-PD-1 from the dose escalation portion of our ongoing phase 1b/2 studies.

Detailed dose escalation results from these trials of ADG126 in combination with either toripalimab or pembrolizumab were later presented at the American Association for Cancer Research (AACR) Annual Meeting in April 2023, along with updated findings from our ongoing monotherapy evaluation. In totality, the data support best-in-class safety and differentiated efficacy profiles for ADG126 both as monotherapy and in combination with anti-PD-1, with potential to overcome the safety challenges of anti-CTLA-4 therapy and become a cornerstone of cancer care by its T cell priming and strong Treg depletion in the TME. As our clinical program advances, we expect the best-in-class safety profile of ADG126 to translate into enhanced clinical benefit by dosing ADG126 at higher levels more frequently in combination with anti-PD-1.

Summary of Clinical Studies & Results

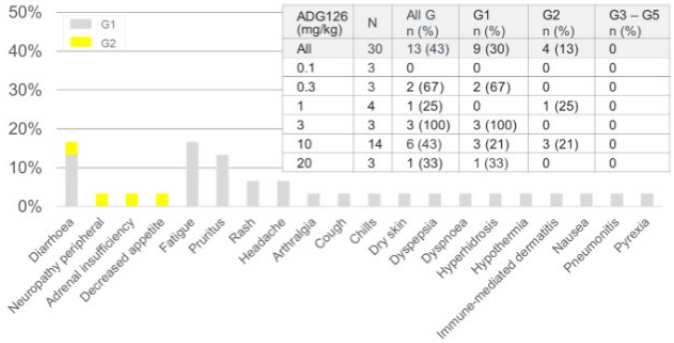
In March 2021, we initiated a Phase 1 trial of ADG126 (ADG126-1001) as monotherapy to evaluate safety and determine a RP2D in patients with advance metastatic tumors, using a traditional “3+3” dose escalation design. A secondary objective of the trial is to evaluate preliminary efficacy based upon anti-tumor activity both as monotherapy and in combination regimens.

In October 2021, we initiated a second monotherapy trial of ADG126 following NMPA approval to start an ADG126 Phase 1 trial in China (ADG126-1002), designed to further support our global clinical development program and pave the way for combination studies of ADG126 in China.

During 2022, we completed monotherapy dose escalation of ADG126 up to 20 mg/kg in both trials, and we initiated monotherapy dose expansion cohorts at 10 mg/kg in the ADG126-1001 trial. Patients received continuous dosing, and we observed favorable pharmacokinetic activity compared to our unmasked anti-CTLA-4 antibody, ADG116. ADG126 has shown a best-in-class safety profile in clinic, consistent with preclinical evaluation enabled by the broad species cross-reactivity of ADG126, including GLP toxicology data.

In September 2022 and April 2023, we presented these clinical results from our ADG126 monotherapy evaluation at the ESMO and AACR annual meetings, respectively. The presentation at AACR included a larger number of patients (N=30) and further reinforced the compelling, best-in-class safety profile at dosing levels up to 20 mg/kg in a heavily pretreated patient population (majority received ≥3 prior lines of therapy) once every three weeks with repeat dosing. No Grade 3 or higher TRAEs were reported. The following chart summarizes the most common TRAEs and their incidence across dose levels:

ADG126 Monotherapy: Best-in-class Safety Profile up to 20 mg/kg with Repeat Dosing*



ADG126 (mg/kg)	N	All G n (%)	G1 n (%)	G2 n (%)	G3 – G5 n (%)
All	30	13 (43)	9 (30)	4 (13)	0
0.1	3	0	0	0	0
0.3	3	2 (67)	2 (67)	0	0
1	4	1 (25)	0	1 (25)	0
3	3	3 (100)	3 (100)	0	0
10	14	6 (43)	3 (21)	3 (21)	0
20	3	1 (33)	1 (33)	0	0

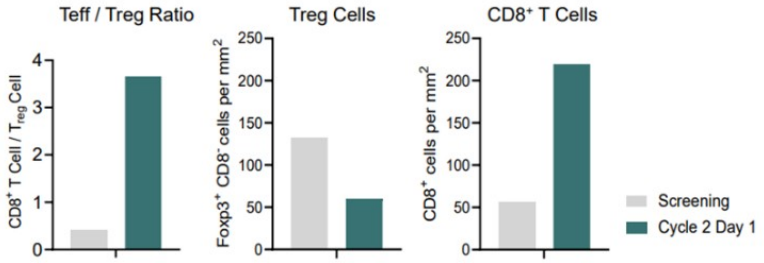
* Results as of the 2023 AACR Data Cut-off Date

Monotherapy data also showed the disease control rate was 37% among 27 evaluable patients across dose levels. Prolonged stable disease was observed in five patients, including an ovarian cancer patient treated at 1 mg/kg with and tumor shrinkage (22% reduction in sum of target lesions) and stable disease observed after 22 cycles. Previously, this patient had surgery and five prior lines of systemic therapies. Additionally, tumor shrinkage (12% reduction in sum of target lesions) was observed in a non-small cell lung cancer patient (NSCLC) who received 14 cycles of ADG126 at 20 mg/kg. Previously, this patient was treated with pembrolizumab and docetaxel.

Our monotherapy evaluation of ADG126 has also increased our understanding of its MOA and our masking technology in clinic. For example, at ESMO 2022, we reported that ADG126 plasma pharmacokinetics (PK) were approximately linear and activated ADG126 accumulated steadily during repeat dosing across different dose levels. This analysis suggests prolonged exposures of activated ADG126 in the tumor microenvironment (TME), with cleaved ADG126 on average accumulating ≥3-fold during repeat dosing, associated with the longer half-life of total ADG126 compared with its parental antibody.

Further, analysis of a clinical sample from a hepatocellular carcinoma (HCC) patient previously treated with atezolizumab and bevacizumab and then followed by lenvatinib demonstrated about nine-fold Teff/Treg improved ratio after dosing relative to before dosing due to reduction in Treg and improvement in T effect cells. These data support the mechanism of action for ADG126 as shown below in data presented at AACR 2023:

ADG126 Monotherapy Tumor Biopsy: Case Study Shows Increased Teff / Treg with Treg Depletion in TME of an HCC Patient who Progressed on Atezolizumab + Bevacizumab*



* Data from paired tumor biopsies were collected before and after treatment. Multiplex immunofluorescence analysis was performed by Dr. Joe Yeong's lab at IMCB, A*STAR. Images were analyzed using HALO. Tregs were defined as Foxp3+ CD8- cells. Teff cells were defined as CD8+ T cells.

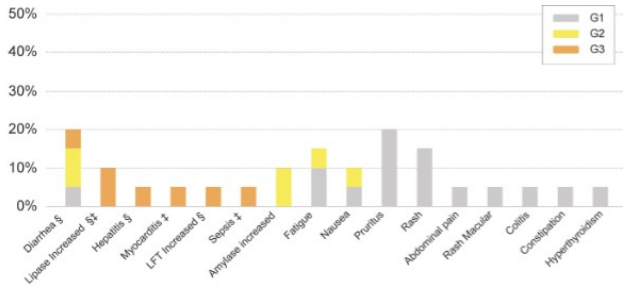
During 2022, we also advanced our phase 1b/2 combination trials for ADG126 with anti-PD-1. In March 2022, we received clearance from the FDA to initiate a new Phase 1b/2 trial to evaluate ADG126 in combination with pembrolizumab (ADG126-P001/KEYNOTE-C98). We are conducting the trial at multiple sites in the U.S. and APAC. In parallel, as part of the ongoing ADG126-1001 trial, a combination dose escalation was initiated to evaluate ADG126 with toripalimab.

In April 2023, we presented data from the dose escalation portion of these studies of ADG126 in combination with anti-PD-1 treatments at AACR. The results reinforced the best-in-class safety profile of ADG126 at doses from 6 mg/kg up to 10 mg/kg. The combination was well tolerated with no dose-limiting toxicities observed with repeat cycles, including in patients who received four or more cycles in the combination cohort with toripalimab.

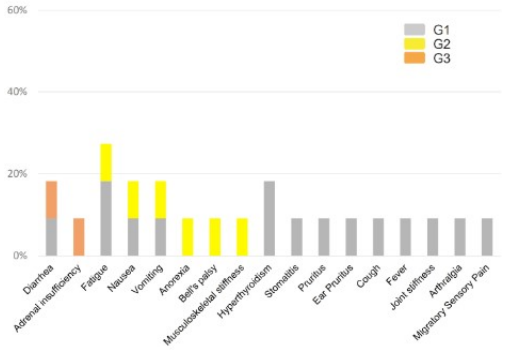
Across 31 patients in combination dose escalation cohorts of ADG126, a total of seven (22.6%) Grade 3 TRAEs were reported, suggesting a safety profile comparable to anti-PD-1 monotherapy and a best-in-class safety profile in combination with anti-PD-1, even at much higher doses. This has been achieved without aggressive safety management for immune-mediated diarrhea/colitis, such as infliximab infusion**.**

The following charts summarize the safety profile from our studies of ADG126 with two different anti-PD-1 therapies, toripalimab and pembrolizumab, as presented in posters at AACR 2023:

Combination Safety: TRAEs for ADG126 with Toripalimab (N=20)



Combination Safety: TRAEs for ADG126 with Pembrolizumab (N=11)



The early efficacy profile of ADG126 was also demonstrated in these heavily pre-treated patient groups, with clinical responses and tumor shrinkage observed during combination dose escalation. Data presented at AACR summarize patient case studies demonstrating clinical benefit, including three confirmed partial responses and multiple cases of prolonged stable disease with tumor shrinkage in patients who received ADG126 plus anti-PD-1 therapies.

Of note, two cases of significant tumor shrinkage (20% reduction and higher in target lesions) were observed in MSS CRC patients with liver metastasis who received ADG126 plus toripalimab. This aligns with anti-tumor activity in MSS CRC shown with ADG116 NEObody in combination with anti-PD-1 therapy showing reductions in CEA levels. Overall, the results further support our ongoing combination dose expansion cohorts evaluating ADG126 in combination with anti-PD-1 in this indication.

At AACR, partial responses were reported in two patients with anal and penile squamous cell carcinoma who received ADG126 plus toripalimab; the patients experienced 36% and 72% reductions in sum of target lesions, respectively. A third partial response was reported in a patient with metastatic endometrial cancer (MSI-H) who received ADG126 plus pembrolizumab and experienced a 37% reduction in target lesions. All three patients were treated at the 10 mg/kg dose administered every three weeks (Q3W).

In April 2023, after the AACR Data Cut-off, an additional (initial) partial response was reported in an IO-experienced cervical cancer patient who was previously treated with two lines of therapy and had progressed after nine cycles of pembrolizumab (CPS = 1; TMB =24).The patient experienced no Grade 3 or higher TRAEs and showed a 30% reduction in target lesions at the end of eight cycles of treatment with ADG126 (10 mg/kg Q3W) and pembrolizumab (200 mg Q3W), following earlier observation of 13% tumor shrinkage as reported at AACR.

The robust safety of masked anti-CTLA-4 enables continuous dosing with anti-CTLA-4 or ADG126 therapy in combination with anti-PD-1 to drive the efficacy in patients in PD-L1 low expression and PD-1 resistant anti-CTLA-4 therapy.

Clinical Development Plan

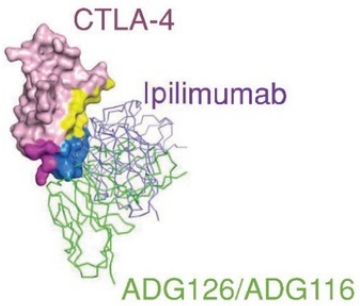
Our clinical development of ADG126 is focused on expanding its safety and efficacy profile in combination with anti-PD-1 therapy. Combination dose expansion cohorts for ADG116 with anti-PD-1 therapies are ongoing, including in MSS CRC to establish proof-of-concept. Additionally, our clinical collaboration with Roche is enabling a randomized, phase 1b/2 clinical trial to evaluate ADG126 in a triple combination in first-line HCC.

ADG126 Background: Mechanism of Action & Preclinical Profile

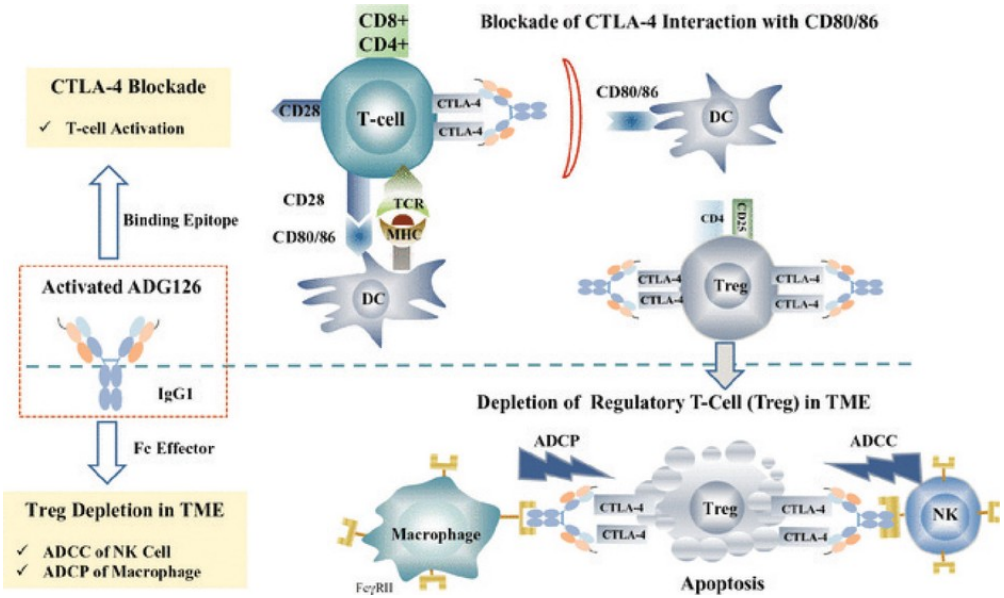
ADG126 is a fully human anti-CTLA-4 mAb. The masking moiety in ADG126 functions to block the interaction between ADG126 and its target CTLA-4 protein. Once ADG126 enters the TME, proteases overexpressed in the TME cleave off the masking moiety, and the antibody is then activated, binding to CTLA-4 and inhibiting its function. ADG126 is locally activated specifically in the TME, rather than systemically, to stimulate antitumor immune response.

In preclinical studies, we observed that ADG126 had an enhanced therapeutic window and improved safety features. Furthermore, in PD studies of ADG126, it was observed that while the CTLA-4 binding affinity was masked in an intact ADG126 antibody, once the masking peptide was cleaved off of ADG126, its high binding affinity to CTLA-4 was restored. In preclinical studies, ADG126 was tolerated at doses of up to 200 mg/kg in nonhuman primate models. We believe the encouraging preclinical tolerability of ADG126 suggests its potential in combination with other immunotherapies such as an anti-PD-1/PD-L1 antibody or an anti-CD137 antibody.

We believe that activated ADG126 potentiates T-cell immune response by blocking the inhibitory effect of CTLA-4. ADG126/ADG116 is designed to target CTLA-4 conserved epitope with species cross-reactivity for translational fidelity.



Moreover, ADG126 has been observed in preclinical animal studies to mediate effector functions to eliminate highly upregulated CTLA-4 expressing cells, particularly regulatory T-cells in the TME, primarily through its strong ADCC. These actions of ADG126 could lead to enhanced activation and proliferation of tumor infiltrating T-effector cells and reduced T-regulatory cell function, which may contribute to a general increase in T-cell responsiveness, including an enhanced antitumor immune response. The below diagram illustrates the MOA of activated ADG126.



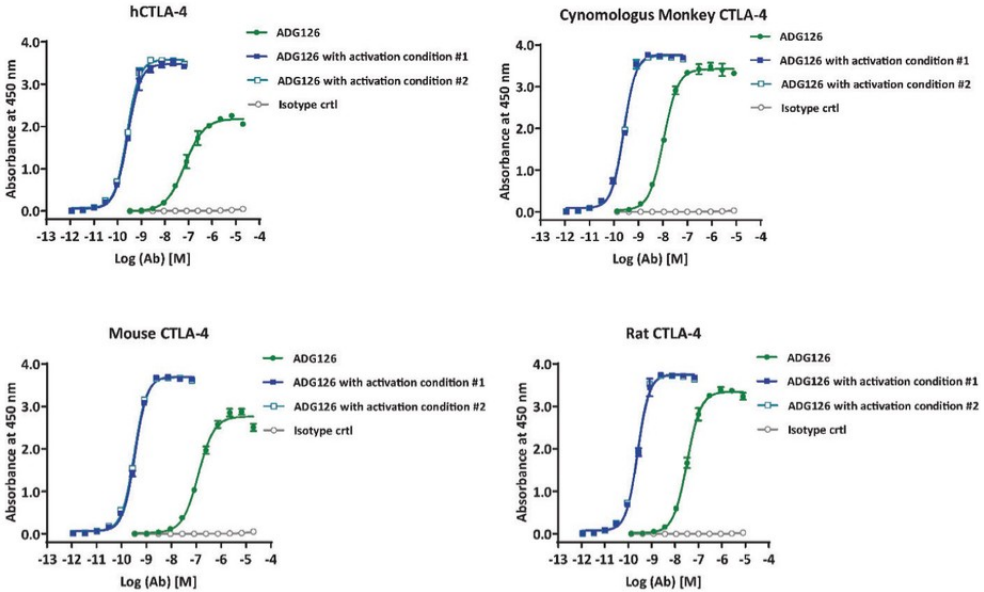
Notes:

“ADCP” refers to antibody-dependent cell-mediated phagocytosis;

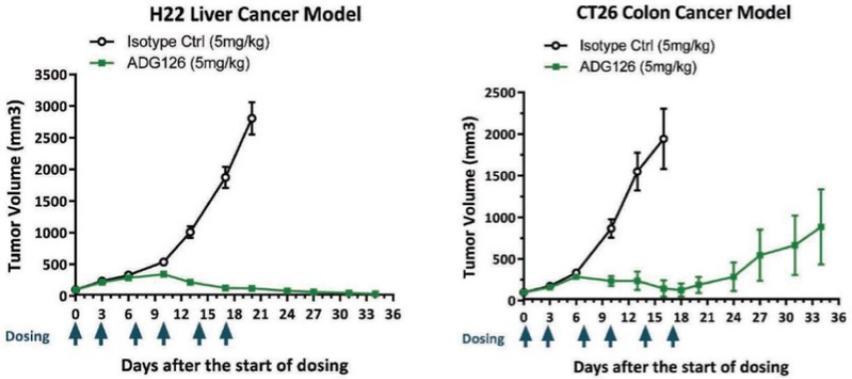
“MHC” refers to major histocompatibility complex;

“TCR’’ refers to T-cell receptor;

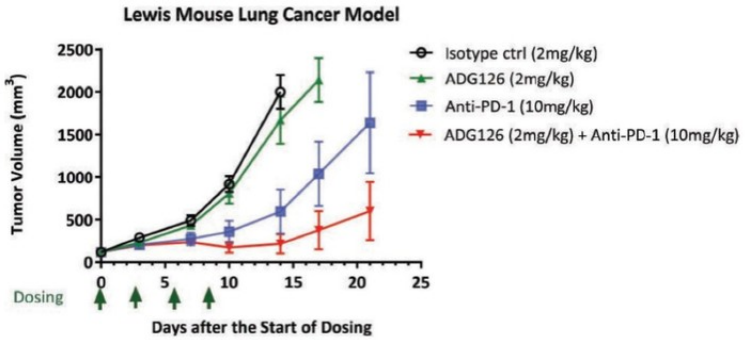
Preclinical Pharmacology: We observed in PD studies that ADG126, in its intact SAFEbody form, bound weakly to CTLA-4. However, once the proteases cleaved off the masking peptide, ADG126 was activated and bound at a high affinity to human, cynomolgus monkey and mouse CTLA-4, as shown in the figures below. Activated ADG126 was observed to lead to the release of CD80/CD86 ligands from CTLA-4 sequestration, and stimulation of CD28 signaling to boost T-cell activity. It also targets regulatory T-cells for depletion within the TME by means of ADCC, to mediate antitumor T-cell immunity.



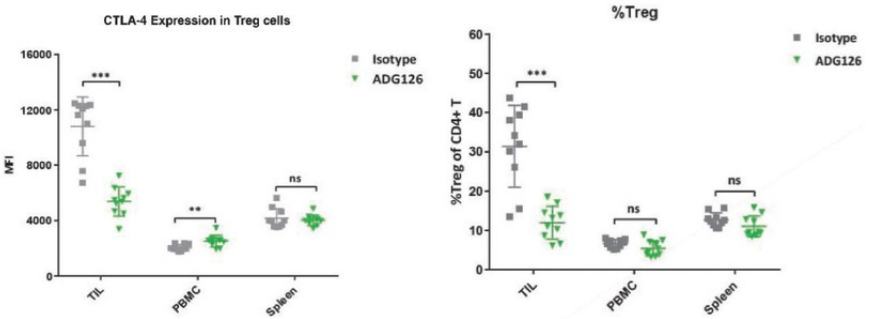
We evaluated the *in vivo* antitumor efficacy of ADG126 in syngeneic mouse tumor models. As shown in the figures below, in these studies, ADG126 was observed to inhibit tumor growth in different mouse tumor models as a monotherapy.



As shown in the figure below, ADG126 synergized with an anti-PD-1 antibody to elicit a stronger anti-tumor response than ADG126 or the anti-PD-1 antibody alone in a Lewis lung cancer model.



ADG126 treatment was observed to specifically deplete regulatory T-cells in the tumor, but not in peripheral tissues. The following figures illustrate the reduction of CTLA-4 expression in infiltrating lymphocytes, or TILs (see figure below on the left) and regulatory T-cell depletion (see figure below on the right) by ADG126 in CT26 tumor model.



Note: "Treg" refers to regulatory T-cells

Preclinical Toxicology: We performed preclinical toxicology studies designed to assess the toxicity features of ADG126. We selected cynomolgus monkeys and mice as toxicology species for animal toxicity evaluation. No abnormal findings attributable to ADG126 were observed. We utilized a nonobese diabetic mouse model to determine percentage of survival with AD126 treatment. All mice survived after six treatments of ADG126 at 50 mg/kg.

In a four-week GLP repeat-dose toxicology studies, intravenous infusion of ADG126 to cynomolgus monkeys at 5, 30, or 200 mg/kg/dose once weekly for five doses followed by a 28-day recovery period was well-tolerated. Adverse, but reversible, microscopic findings of minimal to moderate mixed perivascular infiltrates were observed at 200 mg/kg in both sexes in the kidney, liver, pancreas, epididymis, skin, and were observed in the ovaries in females, and the connective tissue associated with the mesenteric lymph node and thyroid gland. The NOAEL was considered to be 30 mg/kg/dose and the highest non-severely toxic dose was considered to be 200 mg/kg/dose.

About CD137

CD137 stimulates the immune system to attack cancer cells and is a key driver for T-cell and natural killer cell, or NK cell, proliferation. ADG106 is designed to target a unique conserved epitope of CD137 with a novel MOA for CD137 agonism by its natural ligand-like binding and cross-linking by Fcy receptors. The broad species cross-reactivity of ADG106 observed in preclinical studies has enabled us to explore robust translational studies concerning the biology of CD137 in mouse, rat, nonhuman primate, and human, especially for anti-CD137 as a single agent and in combination therapies in immuno-competent syngeneic tumor models. CD137 is a member of the tumor necrosis factor, or TNF, receptor superfamily. The binding of an antibody to this receptor induces a co-stimulatory signal on activated enhanced cytotoxic T lymphocyte, or CD8+ T-cells, and natural killer, or NK cells, resulting in proliferation, and increased pro-inflammatory cytokine secretion and cytolytic function. CD137 co-stimulation is a clinically validated pathway for T-cell activation and its antitumor response is highlighted by the approval of a CD137-targeting CAR-T therapy by the FDA. Because most tumors are killed by cytotoxic T-cells in an antigen specific manner, we believe agents that mediate CD8+ T-cell activation can impart strong cytolytic activity. Therefore, we believe that CD137 agonists are promising candidates with potential to enhance and mediate long lasting antitumor immunity.

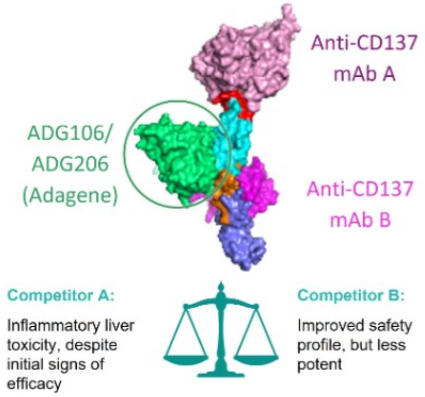
CD137: Our Solution

Our two anti-CD137 antibody candidates target a unique epitope of CD137 to balance the safety and efficacy of anti-CD137 therapies (see figure below).

ADG106 is designed to target a unique conserved epitope of CD137 with a novel MOA for CD137 agonism by its natural ligand-like binding. ADG106 has not been observed to bind to unstimulated naive T-cells, which have no detectable level of CD137 expression. ADG106 is also designed to bind to activated NK cells to boost their cytotoxic and ADCC functions.

ADG106 can also mediate cross-linking via Fc receptors, which are critical for its activity. Our next generation anti-CD137, ADG206 IgG1 POWERbody features Fc-engineering to enhance the cross-linking. With further addition of our SAFEbody precision masking technology, ADG206 is poised to power the efficacy of anti-CD137 therapies (4-fold higher preclinical potency than urelumab analog), while ensuring the safety via conditional activation by pushing the boundaries of prior anti-CD137 agonistic approaches.

ADG 106/206 target a unique epitope of CD137/4-1BB pathway validated by CAR-T



ADG106 NEObody: A Novel Agonistic Anti-CD137

ADG106, is a fully human ligand-blocking, agonistic anti-CD137 IgG4 mAb generated using our NEObody technology to target a unique conserved epitope of CD137.

We previously completed two Phase 1 clinical trials, ADG106-1001 and ADG106-1002, in the U.S. and China, respectively, evaluating ADG106 as monotherapy in a total of 98 patients with advanced or metastatic solid tumors and/or NHL. Our results demonstrated that ADG106 had a well-tolerated safety profile and evidence of single-agent efficacy profile. In preclinical studies, we also observed that ADG106 had encouraging antitumor activity and was well tolerated as a monotherapy and had additive or synergistic effects in combination with the existing standard-of-care, or SOC, and other immuno-oncology therapies.

As monotherapy, ADG106 was well-tolerated at doses of 3 and 5 mg/kg, and at 300 mg and 400 mg flat doses. We also observed tumor shrinkage in some patients, including one patient with nasopharyngeal cancer (NPC) who previously failed multiple therapies and showed a partial response to ADG106 treatment with a 40% tumor size reduction. In addition, two NHL patients showed more than a 30% tumor size reduction. Overall, we observed a significant disease control rate of 56% (45 among 81 patients) for anti-CD137 monotherapy with robust safety profiles, including tumor size reductions in the multiple patients.

Importantly, across all dose cohorts in both trials, we observed three patients with ≥ Grade 3 liver enzyme increase; among them, two patients with ≥Grade 3 AST increase enrolled in ADG106-1001 (treated at 10 mg/kg and 300 mg fixed dose levels), including one patient who had abnormal baseline liver enzyme exhibited Grade 3 AST increase, and one patient enrolled in ADG106-1002 with abnormal liver enzyme baseline showed a Grade 3 AST and ALT liver enzyme increase (treated at 5 mg/kg). These liver enzyme increases were not observed to be dose-dependent.

Clinical Summary: Focus on Investigator-Initiated Trials in Combination Settings

ADG106 is now being evaluated in combination settings in two investigator-initiated trials. The studies are supported by the combined findings of our phase 1 monotherapy trials, data from our extensive preclinical studies, as well as PD marker-based modelling from our prior and ongoing trials. These clinical results indicate that targeting the unique and highly conserved epitope of CD137 by ADG106/ ADG206 has the potential to balance safety and efficacy, thereby addressing the limitations of other existing anti-CD137 agonists that target very different epitopes.

Previously, we evaluated clinical safety and efficacy profiles of ADG106 in combination with anti-PD-1 therapy in patients with advanced solid tumors and relapsed or refractory NHL. Results from the Phase 1b/2 trial in China (ADG106-1008) showed one observed partial response in an NPC patient out of 20 patients enrolled. In August 2022, we announced plans to wind down the ADG106-1008 trial, given prioritization of our anti-CTLA-4 programs and potential of our next generation anti-CD137 therapy, ADG206.

We also observed dose dependent sCD137 changes in blood samples of patients treated by ADG106 in combination with anti-PD-1, further supporting its potential in combination and consistent with observation by other clinical studies. The semi-quantitative analysis and studies conducted suggest the increase of plasma sCD137 or its induction ratio of induced sCD137 over the baseline value is associated with the clinical benefits of NPC patients from stable disease to partial response.

In November 2021, we announced an investigator-initiated trial with the National University Cancer Institute, Singapore and the National Cancer Centre Singapore, in collaboration with the Singapore Translational Cancer Consortium to evaluate ADG106 with another anti-PD-1, nivolumab, in patients with advanced non-small cell lung cancer (NSCLC). The Phase 1b/2 open label trial (ADG106-T6001) is designed to evaluate safety, tolerability, and anti-tumor activity of the combination in up to 53 patients with advanced NSCLC who have progressed after prior treatment. In January 2022, we reported that the trial had enrolled and dosed the first patients. The trial is currently ongoing as of the date of this annual report with plans to present interim results at an upcoming medical conference.

Additionally, in August 2022, we announced a second investigator-initiated trial with the Singapore research consortium. The Phase 1b/2 clinical trial (ADG106-T6002) is evaluating ADG106 in combination with neoadjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel) in up to 66 patients with early-stage, HER2 negative breast cancer. The trial is currently ongoing as of the date of this annual report.

ADG206 POWERbody: A Masked, IgG1 FC-engineered Next Generation Anti-CD137 Therapy

ADG206 is designed to solve the safety and efficacy challenges of anti-CD137 therapy, leveraging the same novel epitope as ADG106 and learnings from development of urelumab (another company’s anti-CD137 targeting antibody), which showed single agent clinical efficacy and dose-dependent liver toxicity in clinic.

In April 2022, we announced preclinical data showing how this, Fc-engineered anti-CD137 agonistic POWERbody incorporates SAFEbody® precision masking technology for conditional activation and is designed to achieve improved safety and efficacy. We reported data from preclinical studies demonstrating that the FcgR-mediated crosslinking of ADG206 in IgG1 format enhances T-cell responses and antitumor activity, while the SAFEbody masking technology secures its activation in the TME to limit on-target off-tumor toxicities.

Preclinical data demonstrated that ADG206 was well tolerated, with normal pharmacokinetic properties and minimal activation in circulation. It also had robust anti-tumor activity as a single agent in multiple tumor models, with 4-fold stronger anti-CD137 agonistic activity of its activated form than a benchmark antibody (analog of urelumab), which is one of the most potent anti-CD137 agonists in development for T-cell co-activation that has demonstrated clinical activity as a single agent but has also shown dose-dependent liver toxicity. ADG206 demonstrated enhanced anti-tumor activity as a single agent and in combination with other checkpoint inhibitors, including anti-PD-1 or anti-CTLA-4 therapy. We believe that the safety and efficacy profiles of ADG206 strongly supports its potential as a combination agent.

In August 2022, following completion of IND enabling studies, we submitted a Human Research Ethics Committee (HREC) regulatory filing in Australia to advance this anti-CD137 POWERbody™, ADG206, into a phase 1 clinical trial in patients with advanced metastatic solid tumors. We have subsequently initiated dosing of the first patient in a phase 1 trial evaluating safety, efficacy and tolerability profiles for ADG206 POWERbody in patients with advanced/metastatic tumors. This next generation anti-CD137 candidate is the first POWERbody candidate to advance into clinic, combining precision masking, Fc-engineering and targeting of a unique epitope to solve the safety and efficacy challenges of anti-CD137 therapies. The phase 1 trial is currently ongoing; pending monotherapy dose escalation results, evaluation in combination settings is planned. For example, it is biologically compelling to combine clinically safe and potent anti-CD137 and anti-CTLA-4 therapies for their synergistic anti-tumor efficacy, but also to ameliorate the toxicity of each monotherapy.

IND-READY CANDIDATES & PRECLINICAL PIPELINE

In addition to our clinical-stage product candidates, we have several IND-ready preclinical candidates and have built a deep, broad and differentiated preclinical pipeline with potential first and best-in-class programs. These programs are in various stages of drug discovery and preclinical evaluation utilizing our three DPL platform technologies NEObody, SAFEbody, and POWERbody.

We currently have multiple differentiated programs undergoing IND-enabling studies, each with robust CMC profiles and compelling preclinical safety and efficacy data. In December 2021, we disclosed the first two of these candidates, ADG152 and ADG153, and reported preclinical data at the American Society of Hematology (ASH) annual meeting. In March 2022, we introduced two additional programs, ADG206 (later advanced into clinical stage) and ADG138, and reported data demonstrating their first and best-in-class potential in conjunction with the American Association for Cancer Research (AACR) annual meeting. Additionally, at AACR 2022, we introduced a new capability for our proprietary bispecific T-cell engagers (TCEs) targeting CD28, which we believe offers a new paradigm and novel approach to overcome the challenges of this target by combining a unique, highly conserved epitope, with our precision masking technology and a tumor antigen targeted TCE for local activation. At AACR 2022, we also presented data for these preclinical candidates to be used as monotherapies or in combination with our CD3 TCEs to achieve safe, powerful and durable immunotherapy.

Additionally, at AACR in April 2023, we presented an additional poster on ADG153, with more comprehensive data showing the candidate’s anti-tumor activity in solid tumor models, as well as target engagement in the tumor microenvironment.

A summary of our pipeline of preclinical programs follows:

- *ADG153:* This masked anti-CD47 IgG1 SAFEbody is differentiated by the novel epitope it recognizes, its strong antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activity, and precision masking for conditional activation. It is designed to realize the full potential of anti-CD47 therapy for both hematologic and solid tumor indications. ADG153 targets a unique epitope with reduced hemagglutination activities in comparison with two benchmark antibodies. It incorporates SAFEbody masking technology to limit on-target off-tumor toxicities and overcome the known safety liabilities of anti-CD47 therapies. The safety mask prevents its rapid clearance by CD47 directed antigen sink effect. Preclinical data demonstrated that ADG153 IgG1 was well tolerated, did not induce human hemagglutination and significantly reduced anemia-related and antigen sink liabilities. In particular, ADG153 IgG1 at a 10 mg/kg dose demonstrated only an 8 percent decrease in red blood cell counts, compared to a 49 percent decrease with a benchmark antibody which is in IgG4 format (analog of magrolimab). After a single intravenous dose, ADG153 IgG1 demonstrated an approximately 8-fold longer apparent half-life and 5-fold higher area under the curve (AUC) at 10mg/kg than the benchmark. Results also showed that ADG153 IgG1 demonstrated greater anti-tumor activity than the benchmark. We believe it is the first anti-CD47 antibody in IgG1 isotype that shows strong ADCC and ADCP effects for tumor killing without serious safety liabilities. ADG153 is currently in the IND-enabling phase.

- *ADG138*: This novel HER2xCD3 POWERbody is masked on both arms with an impressively high therapeutic index relative to its parental non-masked TCE in both HER2 high and low expressing solid tumors including HER2 high resistant/refractory tumors relative to a benchmark antibody (DS-8201, a HER2 targeting antibody drug conjugate commercially available in specific indications). ADG138 preclinical data support its development for HER2-expressing solid tumors as a single agent and in combination with other immune modulating agents. Preclinical data demonstrated the excellent safety profile of ADG138, including 100-fold greater reduction in cytokine release compared to its parental TCE. Results showed that ADG138 has potent anti-tumor activity in HER2 high and low expressing tumors, as well as resistant/refractory tumors. ADG138 also had synergistic anti-tumor activity in HER2 positive tumors when combined with anti-CD137 or anti-PD-1 therapy, or tumor targeted CD28 bispecific antibody. ADG138 is currently in the IND-enabling phase.

- *ADG152:* This CD20xCD3 POWERbody integrates the company's proprietary bispecific TCE platform with SAFEbody precision masking technology to minimize cytokine release syndrome (CRS) and on-target off-tumor toxicities for an increased therapeutic index. The anti-CD20 arm of ADG152 has enhanced the binding to CD20, while its anti-CD3 arm has tailor made affinity for CD3 using SAFEbody technology. In comparison with a benchmarked antibody in clinical development (analog of plamotumab), ADG152 showed improved safety with cytokine release control even at a 100-fold higher dose than the benchmarked antibody analog and 2- to 3-fold prolonged half-life than the benchmarked antibody analog in exploratory preclinical monkey studies. In preclinical mouse xenograft tumor models, ADG152 demonstrated strong and sustained anti-tumor activity, with almost complete tumor growth inhibition when dosed at 1.5 mg/kg. ADG152 is currently in the IND-enabling phase.

- *CD28 T-cell engagers:* We are developing anti-CD28 bispecific POWERbody TCEs that exhibit enormous potential to fulfill the promises of safe and durable T-cell mediated synergistic immunotherapies when combined with CD3 bispecific POWERbody TCEs and/or checkpoint inhibitors. Enabled by our suite of antibody platform technologies, preclinical data demonstrated the potential to mitigate the serious safety concerns of CD28 activation and make custom designed antibodies targeting a highly conserved epitope with broad species reactivity. We currently have multiple tumor associated antigen (TAA)xCD28 POWERbodies in preclinical development, such as B7-H3xCD28 and HER2xCD28, which can also be combined with our CD3 TCEs to achieve safe, powerful and durable immunotherapy for solid tumors through combination of the fundamental mechanisms and pathways across the cancer immunity cycle. For the avoidance of doubt, as of the date of this annual report, the CD28 T-cell engagers have not entered into IND-enabling stage.

OUR PLATFORM

Overview

Our proprietary DPL platform is built upon our insights into precise and dynamic antibody-antigen interaction. As such, our DPL platform has been designed to enable the discovery of antibodies with better developability properties. By addressing the challenges in traditional antibody design and engineering, we believe that our DPL platform will enable us to improve the efficacy and safety profile of antibody therapeutics. Our DPL platform is empowered by our computational platform, artificial intelligence and three innovative technologies: NEObody, SAFEbody, and POWERbody.

Life is motion: *Harnessing the Dynamic Power of Antibodies*

The motion of proteins and their dynamic interactions trigger a cascade of complex biological and pharmacological effects. Our core technology is built upon our fundamental understanding of the role that protein folding and the motion of molecules play in giving rise to dynamic conformational diversity, where an amino acid sequence can adopt multiple structures and functions. Our approach recognizes that a protein's native state is not accurately represented by a single static structure but rather by a variety of structures in dynamic equilibrium, resulting in a high level of functional diversity, in contrast to the conventional static antibody drug discovery paradigm of "one sequence, one structure and one function." We have developed our proprietary AI-Powered DPL platform to explore the dynamic conformational diversity of protein sequences, and the flexible binding sites of antibody sequences in particular, as a new paradigm for antibody drug discovery. Our DPL platform combines artificial intelligence, or AI, algorithms and ever-increasing big data in antibody sequence, structure, binding epitope and affinity from public and our own proprietary databases to design, construct and screen high-quality proprietary antibody libraries with well-defined sequence, scaffold and biophysical attributes for antibody drug discovery. Powered by computational physics in combination with AI and big data, our DPL platform samples a potentially infinite number of dynamic binding interface structures arising from the conformational diversity of a finite number of antibody amino acid sequences, allowing us to exponentially expand the universe of candidate antibody binding sites far beyond conventional natural or synthetic antibody repertoires. By exploiting conformational diversity, we have designed and precisely constructed approximately one trillion (10^{12}) antibody sequences in our DPL. These antibodies feature broad epitope (the portion of an antigen that are recognized by an antibody) coverage and robust chemistry, manufacturing, and control, or CMC, attributes.

We believe our AI-powered antibody discovery and engineering DPL platform significantly increase R&D productivity for antibody drug discovery, as illustrated by our clinical and preclinical pipeline. For example, DPL library screening against CTLA-4 or CD137 antigens has yielded a large number of high affinity primary hits. The abundant discovery hits with diversified binding epitopes show the power of our AI-powered DPL platform not only in creating novel antibodies in targeting different epitopes of a given antigen, but also in targeting the conserved epitope across different species of a given antigen with broad species cross-reactivity from human, monkey to mouse, which enables us to study their efficacy and safety in extensive immuno-competent or syngeneic animal models, to explore their pharmacodynamics and predictive biomarkers in responding vs nonresponding tumor models in vivo, and to understand their deep target biology and novel MOA before testing them in human clinical trials to look for their clinical signals consistent with their MOA. Our DPL platform empowers us to engage the dynamic epitope of the conformationally dynamic target which might be challenging using conventional antibody discovery approaches. We believe that the high-affinity and cross-reactive primary hits from our AI-Powered DPL library screening save time and cost from discovery to early clinical proof of concept. The broad species cross-reactivity of the primary hits also streamlines lead identification and potentially enables high fidelity translation from preclinical to clinical studies. Furthermore, we believe our AI-powered dynamic precision library expands the diversity at the start of discovery to maximize the chance that suitable leads are found on the first pass.

Translational fidelity from preclinical modeling to informed clinical development is one of the top challenges to developing cancer immunotherapies. Most traditionally developed antibodies do not cross react between their human and murine targets due to their limited species cross-reactivity, making it very difficult to reliably evaluate the same antibody in both the preclinical and clinical settings. Some of the most contentious issues related to preclinical and clinical studies of the targets of our clinical-stage product candidates, immunotherapies are traceable to the differences between the antibodies used for preclinical and clinical studies. For example, we believe our clinical stage anti-CTLA-4 and anti-CD137 candidates bind to different epitopes and exhibit dramatic differences in their respective clinical safety and efficacy results, underscoring the importance of finding suitable species cross-reactive antibodies like those we have utilized for comprehensive preclinical evaluation before entering clinical trials.

We believe that it is essential to model the interactions between tumors and an intact host immune system *in vivo* to evaluate the therapeutic potential of antibodies in preclinical studies. The flexibility of antibody binding interface is fundamental to the NEObody technology of our DPL Platform and allows us to generate species cross-reactive antibodies to assess the safety and efficacy potential of mono- and combination therapy candidates in syngeneic animal models before launching clinical trials. We use syngenic animal models which are known for their intact *in vivo* immune systems to provide the original proof of concept for cancer immunotherapies by blocking immune check points with monoclonal antibodies, or mAbs. We believe that the use of species cross-reactive antibodies, rather than surrogate antibodies used in traditional syngeneic mouse models, should facilitate the translational relevance and clinical utility of these well-established preclinical models for determining optimal dose, schedule, sequencing, combination synergy, risk and benefit features. The results from the assessment of new species cross-reactive antibodies in rigorous preclinical models may allow us to control the scope and cost of clinical trials, enable the identification of potential clinical biomarkers useful to monitor clinical pharmacological and safety signals, and help preselect patients for precision mono- and combination therapies.

AI-Powered Antibody Discovery

We believe that efficient drug discovery requires significant commitment to resolve three key challenges: 1) the selection of targets with preclinical and/or clinical validation; 2) the availability of abundant hits at discovery stage for the identification of Pre-Clinical Candidates, or PCC, that usually takes a highly iterative process from target-to-hits, lead identification and lead optimization; and 3) deep understanding of target biology and MOA from detailed molecular, cellular, *in vivo* preclinical and human disease models. To address these challenges and to improve antibody R&D productivity, we have designed and built our AI-powered DPL platform to provide sufficient discovery capacity, capable of generating abundant high quality hits against targets, and then selecting the right leads for extensive preclinical testing in order to understand their MOAs, their efficacy and safety potential before going for clinical proof of concept testing.

We believe that it is critical to pair the right PCC with the specific epitope of a chosen target. The affinity and precise orientation by which the specific epitope of a given target is engaged by the PCC can have a profound impact on the pharmacology and toxicity of drug candidate. Therefore, we believe precision design and engineering of antibody-based drugs make a fundamental difference on the success of a drug discovery program. As demonstrated by extensive preclinical and early clinical data for our three clinical programs targeting a conserved epitope, across humans, monkeys and mice can give rise to novel biological and pharmacological activities. The broad species cross-reactivity of our candidates can facilitate seamless translational studies from different immune-competent syngeneic tumor models to monkeys, and then subsequent clinical trials in humans. The novel MOA and biology concerning targets such as CTLA-4 and CD137 include their regulation in peripheral and tumor microenvironments, the involvement of different immune cells upon target engagement such as T-regulatory cells by anti-CTLA-4 specific antibodies ADG116 and ADG126 and NK cells by anti-CD137 ADG106. We believe these examples provide strong support for our proposal to search for “The Right PCC” that is paired with the specific epitope of a given target in order to unlock the biology of such target and its pathway and to facilitate a deep understanding of its MOA in triggering a cascade of biological and pharmacological events leading to disease control.

In order to search for “The Right PCC,” our proprietary DPL platform uses a deep learning approach to explore the conformational diversity of antibody binding sites. Our DPL platform combines AI algorithms and ever-increasing big data in antibody sequence, structure, and binding epitope and affinity from public and our own proprietary databases to design, construct and screen high-quality proprietary antibody libraries with well-defined sequence, scaffold and biophysical attributes for antibody drug discovery. Our computational engine combines software, AI and visualization tools to mine, organize, compute, and interactively explore these immense multidimensional big data sets. We iteratively inform wetlab experimentation with *in silico* computation, and vice versa. By exploiting conformational diversity through the combination of our proprietary computational algorithms with AI, we have designed and precisely constructed approximately one trillion (10^{12}) antibody sequences in our DPL. These antibodies feature broad epitope (the portion of an antigen that are recognized by an antibody) coverage and robust CMC attributes. The antibodies discovered can be further engineered into NEObody, SAFEbody and POWERbody antibodies depending on the targeted product profile of a given therapeutic target.

Our three clinical programs illustrate how our AI-powered DPL platform has improved our R&D productivity. Our DPL library is a large physical phage library (~10^{12}) that contain our AI-powered synthetic designer antibodies with flexible antibody binding interface. The combination of binding interface flexibility with the variation of amino acid sequences in the antigen binding interface exponentially increases the conformational diversity of our AI-powered DPL libraries, far beyond conventional natural or synthetic antibody libraries. Our AI-Powered DPL library screening against target antigens have yielded a large number of high affinity primary hits. For example, the anti-CTLA-4 antibody ADG116, was identified from 74 high affinity primary hits with a wide range of epitope diversity in terms of their species cross-reactivities: 19 clones are human, monkey, canine and mouse cross-reactive; 12 clones are human and monkey cross reactive but weak mouse cross-reactive; 32 clones are human and monkey cross-reactive; 11 clones only recognize human CTLA-4. The abundant discovery hits with diversified binding epitopes for varying degree of species cross-reactivity show the power of our AI-powered DPL platform not only in creating novel NEObodies in targeting different epitopes of a given antigen, but also in targeting the conserved epitope across different species of a given antigen to enable translational studies from immune-competent animal tumor models to human patients due to their broad species cross-reactivities.

We believe that the high affinity and species cross-reactive primary hits from our DPL library screening saves time and cost from primary hits to straight PCC. The broad species cross-reactivity of the primary hits also streamlines lead identification through simple syngeneic tumor models for safety and efficacy testing. The robust CMC attributes of our DPL library are designed to also eliminate the requirement to optimize antibody sequences before starting CMC process for IND enabling and formulation studies. Furthermore, we believe our AI-powered dynamic precision library of approximately one trillion (10^{12}) antibody sequences expands the diversity at the start of discovery to maximize the chance that suitable leads are found on the first pass. In conclusion, we believe our AI-powered antibody discovery and engineering DPL platform significantly increases R&D productivity for antibody drug discovery. It has enabled us to generate highly differentiated PCC molecules that we believe can target the conserved epitope across different species for novel MOAs and also facilitate seamless translational studies from animals to human via their broad species cross-reactivity.

Briefly, our AI-powered antibody discovery engine includes six steps:

1. First principle of antibody folding and dynamics. We fold the antibody primary amino acid sequence into three-dimensional structures based on machine learning or homology modeling in combination with the Molecular Dynamic Simulation in the presence and absence of dynamic interaction with their antigen targets.

2. AI-powered deep learning of antibody sequence and structure and binding epitopes. AI algorithm and machine learning have been widely used to map protein sequence and structure variation and connectivity. Deep learning has been used to map the antibody and antigen epitope in order to learn the landscape of the epitope space and their correlation with antibody binding interface.

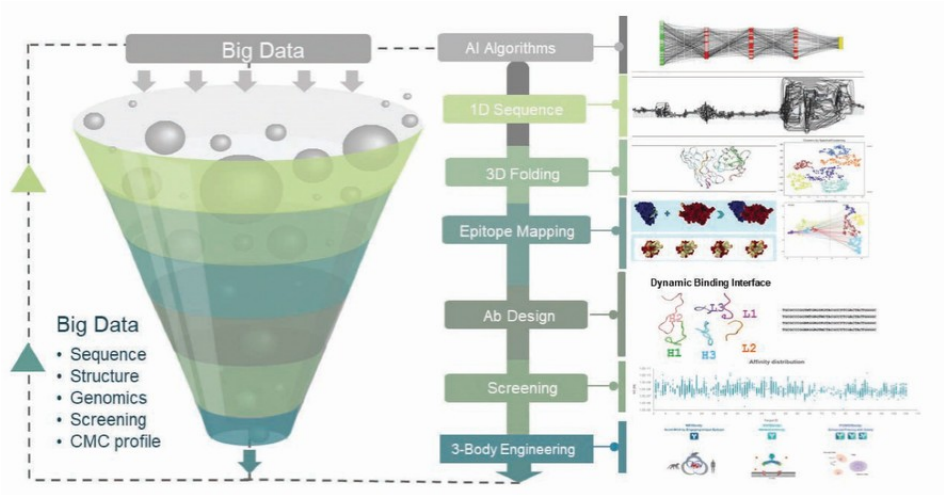
3. Antibody design that combines the conformational diversity with primary amino acid sequence variation. We have designed antibody libraries that contain dynamic binding units and their combination in the context of different CDRs and framework scaffold to capture their conformational diversity of antibody binding interface in combination with variation in primary amino acid sequences far beyond conventional natural or synthetic antibody libraries.

4. Synthetic dynamic precision library by AI-powered computational design. The amino acid sequence library is converted into synthetic DNAs that can be assembled and constructed for phage and yeast library screening.

5. Directed evolution by phage and yeast libraries. The synthetic phage and yeast libraries can be screened semi-automatically for more than 100 antigens to yield high affinity primary hits.

6. PCC identification by targeting conserved epitope with broad species cross-reactivity to unlock the deep biology of target and its MOA upon target engagement by the PCC. PCC is designed and selected to target the conserved epitope of a given target across different species. Traditionally, affinity of primary hits from synthetic antibody libraries have to be improved before subjecting them to extensive in vitro and in vivo assays for lead identification and optimization through an iterative process between functional assays and antibody engineering. Our DPL platform can yield high affinity primary hits, which can then become product candidate leads subject to functional characterization without intensive iterative lead optimization process.

The following diagram illustrates how AI algorithms and big data empower rapid antibody discovery with improved productivity:



NEObody™

NEObody technology is a fully synthetic phage display and yeast display-based antibody discovery technology, which we believe is differentiated from other synthetic antibody technologies through its innovative designs and precise constructions. Our designs are based on critical insights gained from extensive studies of antibody structural variability made possible by our proprietary in-house developed computational tools.

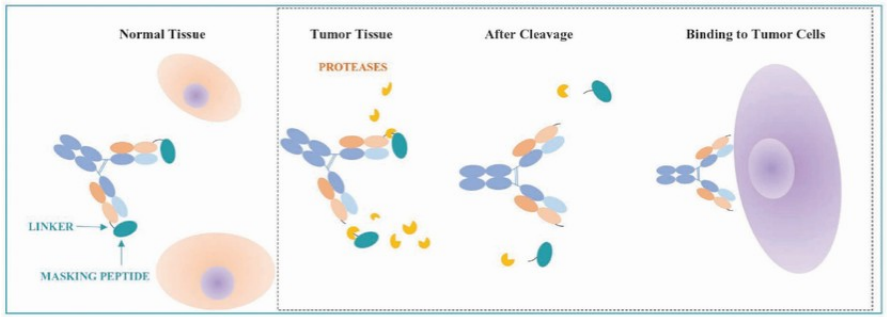
Innovative antibody library design: We believe that diversity of an antibody library should be defined at the quaternary structural level, instead of the traditional primary amino acid sequence level. Comparison of structural and sequence diversity revealed that variability as assessed by structural alignments was generally lower than the variability observed with sequence alignments. Based on our deep understanding of chemical principles governing antibody folding and extensive analysis of a vast number of antibody structural variability, through novel statistical tools developed in-house, we have redefined the antibody hyper-variable regions, or HVRs, that are critical for antigen recognition. These HVRs, as defined based on structural variability, are distinct from but complementary with complementarity-determining regions that are traditionally defined based on amino acid sequence variability. In addition, we have defined and designed dynamic motifs which adopt multiple conformations and incorporated them into our DPL antibody library design to enable the coverage of a wide range of structural diversity with a limited number of amino acid sequences.

Broad epitope coverage, particularly of evolutionarily conserved epitopes: NEObody technology enables us to discover antibodies targeting numerous epitopes against a broad range of antigens. In particular, we focus on the antibodies targeting the conserved epitopes of divergent antigens. These species cross-reactive antibodies not only have the potential to reveal new biological functions of the targets, but also facilitate preclinical studies using various immune intact animal models, resulting in high fidelity translation from preclinical to clinical studies. Our NEObody technology has been evaluated in preclinical studies with numerous antigens, including some difficult antigens such as membrane or oligomeric proteins. The success criteria in our preclinical assays include high affinity of primary hits with diverse antibody sequences, broad epitope coverage, as well as favorable CMC development properties. For example, ADG106 was discovered using our NEObody technology to target a conserved epitope of CD137 that mostly overlaps with its ligand binding site, which we believe enables ADG106 to activate CD137 in its natural ligand-like fashion, with complete blocking of CD137L, which may differentiate it from two other investigational leading CD137 agonistic antibodies.

Enhanced developability profiles: NEObody technology is designed to preemptively eliminate the chemically unstable sites, or combinations of "problematic" sites that may pose risk for downstream manufacturing processes. This precision design strategy coupled with precision oligonucleotides and library construction have resulted in our high-quality antibody discovery libraries. The primary hits from these libraries generally lack severe "problematic" and spurious amino acid sites, and therefore, may offer promising characteristics for further development.

SAFEbody®

SAFEbody is our proprietary differentiated precision antibody masking technology designed to enable an antibody to bind its target specifically only after conditional activation of the antibody in target tissues. By engineering our antibody therapeutic candidates to selectively activate in the TME, our SAFEbody technology is designed to improve safety and tolerability of antibody therapeutics while simultaneously maintaining clinical activity. Through this technology, we believe we can provide a solution to on-target off-tumor toxicity, one of the long-lasting challenges with many approved antibody therapeutics.



Activation in the TME: SAFEbody technology is designed to mask an antibody binding interface with a masking motif, which then prevents an antibody from binding to its target in healthy tissues. The masking motif is designed to activate or unmask the antibody binding in the TME where certain activation conditions such as a protease is upregulated as compared to healthy tissues, allowing the antibody to bind to and attack the tumor. Our SAFEbody enabled therapeutic candidates are therefore designed to be activated predominantly in the TME while remaining largely in an inactive state in healthy tissues.

Innovative masking moiety library design: Leveraging computational biology, we have designed multiple masking libraries with structured scaffolds and balanced chemistry of amino acids with favorable attributes for masking, easier manufacturing processes, and lower immunogenicity.

Precision masking without self-inhibition: To differentiate from other masking technologies, our antibody masking moieties have been designed and discovered in the right context in an effort to provide greater expression and specificity with no self-inhibition upon activation. We employ sophisticated screening processes for rapid discovery of highly masked SAFEbody product candidates subject to systematic tuning of the masking efficiency to match the target biology.

Improved pharmacology and safety features: We believe our SAFEbody technology has the potential to also reduce the dose-limiting toxicities observed in combination therapies and thus potentially enable new combinations with other cancer therapies that were previously difficult to use. Our SAFEbody technology may also provide favorable for PK and PD profiles for antibodies and ADCs to reduce the drug clearance from circulation in healthy tissues.

Our SAFEbody technology has been applied to multiple target antibodies that have been either discovered with NEObody technology or supplied by our partners. Our ADG126 was discovered by combining SAFEbody technology with its parental antibody discovered through our NEObody technology.

POWERbody™

In recent years, multiple modalities have been developed to enhance the potency of traditional antibody drugs. These include Fc engineering for enhanced ADCC or cross-linking efficiency, ADCs and TCEs. Some of them, such as TCEs, can be so potent that only micrograms of the active ingredient are needed for a single dose, in contrast to regular antibody where hundreds of milligrams or even grams are required for a single dose. NEObodies can be converted into SAFEbodies which can be further reformatted into SAFEbody ADCs, bispecific TCEs, and Fc engineered antibodies. We refer to these to as POWERbodies to indicate their potentially enhanced potency and safety profile.

We believe SAFEbodies can be applied to these modalities. Since an unmasked ADC, TCE, or Fc engineered antibody can be so potent, there is the risk that it will cause severe toxicity due to damage to healthy tissues or fast lysis of tumor cells, resulting in a narrow therapeutic window, as is frequently observed with some ADC drugs or TCEs that have been FDA approved or are in clinical development. We believe our POWERbodies enabled by our SAFEbody technology with ADC, TCE, etc., due to their inactivity in circulation and specific local activation in TME, could significantly reduce toxicity and at the same time retain efficacy.

POWERbody technology aims to boost the efficacy of antibody candidates with safety profiles enhanced by our SAFEbody technology. We believe our POWERbody technology will unleash the full power of antibody-based therapeutics to kill cancer cells with enhanced safety, achieving full potential in antibody-based therapies such as bispecific TCEs and ADCs.

CLINICAL COLLABORATION AGREEMENTS

To further advancement of our pipeline, we have put in place various clinical collaborations with pharmaceutical companies and academic or research organizations. We completed several such agreements to support the clinical evaluation of our wholly-owned pipeline candidates. These include:

- In December 2022, we announced a clinical trial collaboration agreement with Roche to evaluate the triple combination of our ADG126 with Roche's atezolizumab and bevacizumab in first-line treatment of advanced hepatocellular carcinoma (HCC). The collaboration will utilize Roche's MORPHEUS-LIVER platform for rapid and efficient combination development. Under the collaboration, Roche will sponsor and conduct a randomized phase 1b/2 multi-national trial to evaluate the efficacy, safety and pharmacokinetics of ADG126 in combination with bevacizumab and atezolizumab, versus atezolizumab and bevacizumab alone, initially in 60 patients. Each company is supplying its respective anti-cancer agent(s) to support the trial. We will retain global development and commercialization rights to ADG126. We believe this trial reflects Roche's leadership and commitment to HCC, where they pioneered the established standard-of-care doublet combination. We also believe it validates Adagene's differentiated ADG126 anti-CTLA-4 clinical program.

- In August 2022 and October 2021, we announced agreements with research organizations in Singapore for an investigator-initiated trials of our ADG106 clinical candidate with neoadjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel) in early-stage, HER2 negative breast cancer and in combination with anti-PD-1 therapy in patients with advanced non-small cell lung cancer (NSCLC), respectively. Both of these ongoing phase 1b/2 clinical trials (ADG106-T6001 and ADG106-T6002) are being conducted at the National University Cancer Institute, Singapore and the National Cancer Centre Singapore, in collaboration with the Singapore Translational Cancer Consortium.

- In July 2021, we entered into two clinical collaborations with Merck, a leader in immuno-oncology. The clinical collaboration and supply agreements include two open-label, dose escalation and expansion clinical studies to evaluate our anti-CTLA-4 mAb product candidates, ADG116 and ADG126, in combination with pembrolizumab for patients with advanced/metastatic solid tumors, respectively. Under terms of the agreement, Merck provides pembrolizumab and input on our clinical trials evaluating pembrolizumab in combination with ADG116 and ADG126, respectively.

TECHNOLOGY COLLABORATIONS WITH BIOPHARMACEUTICAL COMPANIES

We enter into collaborations with biotechnology and pharmaceutical companies to leverage the power of our technology platforms, creating a network of potential future revenue streams that complements future long-term value from our wholly-owned pipeline. These collaborations include both technology licensing agreements and outlicensing of product candidates, which allow us to retain significant future participation in product sales through royalties paid on net sales. In the future, we may also enter into strategic collaborations for our preclinical and clinical assets to both accelerate the path to clinic and drive global commercialization.

Previously, we have entered into technology licensing agreements with Sanofi, Exelixis and ADC Therapeutics to develop antibody-based therapeutics against tumor targets using our SAFEbody technology. We have also out-licensed the Greater China rights for two antibody candidates to Dragon Boat Pharmaceuticals and its affiliates. Additionally, we have leveraged our DPL technology platform and antibody discovery and engineering capabilities in discovery efforts with the NIH, and Mitsubishi Tanabe, Celgene (now BMS) and GSK.

Our technology collaborations enable growth by generating cash flow and revenues that partially offset expenditures on our internal research and development programs, expanding our knowledge base regarding our antibody technologies across multiple targets and antibodies provided by our partners, and providing us with future joint development opportunities.

Below are the highlights of those collaborations with our business partners:

Sanofi Collaboration and Technology License Agreement

In March 2022, we entered into a collaboration and license agreement (the “Sanofi Agreement”) with Genzyme Corporation, a wholly-owned subsidiary of Sanofi (“Sanofi”), pursuant to which we agreed to generate masked monoclonal and bispecific antibodies for development and commercialization by Sanofi with our SAFEbody technology. Under the terms of the agreement, Adagene will be responsible for early-stage research activities to develop masked versions of Sanofi candidate antibodies, using Adagene’s SAFEbody technology. Sanofi will be solely responsible for later stage research and all clinical, product development and commercialization activities.

Pursuant to the Sanofi Agreement, we granted Sanofi an exclusive, worldwide, sublicensable license to research, develop, use, make, have made, sell, offer for sale, import and commercialize products containing the masked antibodies to be generated by us.

We are subject to certain exclusivity provisions limiting our right to pursue, engage in, on our own or in collaboration with one or more third parties, directly or indirectly, non-clinical (including pre-clinical research) or clinical development of, commercialization of or manufacture for clinical or commercial use, of any research, develop, make, and commercialize any other antibodies directed to the selected targets for a period of five years, subject to exceptions.

We are required to use commercially reasonable efforts to generate masked antibodies in accordance the program plan for each target at our cost. Sanofi is required to use commercially reasonable efforts to further develop, obtain regulatory approval and commercialize the antibodies at its costs.

Under the Sanofi Agreement, we received a US$17.5 million upfront payment for Sanofi to advance two initial Sanofi antibody candidates in the collaboration, followed by options to intiate for two additional candidates. To exercise an option, Sanofi is obligated to pay an additional fee.

Additionally, we will be eligible to receive total potential development, regulatory and commercial milestone payments of up to $2.5 billion for advancement of the candidates, or US$625 million per program. All four potential candidates in the collaboration will be exclusively developed and commercialized by Sanofi. In addition, we are entitled to receive low to mid-single-digit tiered royalties on global net sales on products developed under the Sanofi Agreement, subject to certain reductions. Royalties, if any, will be payable on a country-by-country and product-by-product basis until the latest of (i) the tenth anniversary of the first commercial sale of such product in such country, (ii) the expiration of the last-to-expire of certain specified patents that cover such product's composition of matter or method of use as sold in such country or (iii) the expiration of regulatory exclusivity for such product in such country.

The Sanofi Agreement will expire upon the termination of all royalty obligations. Sanofi will own the inventions relating to the compounds arising in connection with the Sanofi Agreement and we will own the inventions relating to our platform. Sanofi may terminate the Sanofi Agreement without cause, in its entirety or on a target-by-target basis or on country-by-country basis, upon a specified notice period, and may terminate for safety reasons on a target-by-target basis upon a specified notice period. Either party has the right to terminate the Sanofi Agreement for cause upon the other party's uncured material breach or insolvency. Upon termination of the Sanofi Agreement for any reason, the license granted to Sanofi will terminate.

Exelixis Collaboration and Technology License Agreement

In February 2021, we entered into a collaboration and license agreement (the "Exelixis Agreement") with Exelixis, Inc., pursuant to which we agreed to generate masked antibodies with our SAFEbody technology against two targets selected by Exelixis. Pursuant to the Exelixis Agreement, we granted Exelixis an exclusive, worldwide, sublicensable license to research, develop, make, have made, sell, offer for sale, import and commercialize products containing the masked antibodies to be generated by us with respect to both targets.

In December 2021, we achieved a key milestone in the collaboration for successful nomination of SAFEbody candidates, which triggered a US$3.0 million milestone payment received by Adagene in January 2022. As of the date of this annual report, we have received US$15.1 million in aggregate payments, including an upfront fee of US$11.0 million received in 2021, the milestone fee of US$3 million and an upfront fee of US$1.1 million for an expanded collaboration in SAFEbody discovery received in 2022 under the Exelixis Agreement.

We are subject to certain exclusivity provisions limiting our right to research, develop, make, and commercialize any other antibodies directed to the selected targets during the term of the Exelixis Agreement, subject to exceptions for antibodies with sequence identities that differ by a specified amount. Exelixis is subject to certain exclusivity provisions limiting its rights to research, develop, make, and commercialize any other masked antibodies directed to the selected targets during the term of the Exelixis Agreement, subject to exceptions for antibodies with sequence identities that differ by a specified amount or use different masking technology.

We are required to use commercially reasonable efforts to generate masked antibodies in accordance the program plan for each target at our cost. Exelixis is required to use commercially reasonable efforts to further develop, obtain regulatory approval and commercialize a product for each target.

In addition to the upfront payment of US$11.0 million received in 2021, in the aggregate, we could be eligible to receive up to US$55,000,000 in development milestone payments, among which we have received US$3.0 million in 2022, US$200,000,000 in regulatory milestone payments, and up to US$525,000,000 in sales milestone payments for both targets under the Exelixis Agreement. In addition, we are entitled to receive mid-single-digit percentage net sales-based royalties on products developed under the Exelixis Agreement, subject to certain reductions. Royalties, if any, will be payable on a country-by-country and product-by-product basis, until the latest of (i) the tenth anniversary of the first commercial sale of such product in such country, (ii) the expiration of the last-to-expire of certain specified patents that cover such product's composition of matter or method of use as sold in such country or (iii) the expiration of regulatory or data exclusivity for such product in such country.

The Exelixis Agreement will expire upon the termination of all royalty obligations. Exelixis will own the inventions relating to the compounds arising in connection with the Exelixis Agreement and we will own the inventions relating to our platform. Exelixis may terminate the Exelixis Agreement without cause, in its entirety or on a target-by-target basis, upon a specified notice period, and may terminate for safety reasons on a target-by-target basis immediately upon notice. Either party has the right to terminate the Exelixis Agreement for cause upon the other party's uncured material breach or insolvency, provided that, upon our material uncured breach, Exelixis may elect to instead continue the Exelixis Agreement, and any subsequent milestones or royalty amounts payable to us after such time will be reduced by a specified percentage. Upon termination of the Exelixis Agreement for any reason, the license granted to Exelixis will terminate.

ADC Therapeutics Agreements

In April 2019, we entered into a material transfer and collaboration agreement (the "ADCT Collaboration Agreement") and a license agreement (the "ADCT License Agreement") with ADC Therapeutics, a late clinical-stage oncology-focused biotechnology company pioneering the development and commercialization of targeted ADCs.

ADCT Collaboration Agreement

Pursuant to the ADCT Collaboration Agreement, we agreed to generate masked antibodies with our SAFEbody technology that could be combined with the pyrrolobenzodiazepine-based cytotoxic payload used in ADC Therapeutics' ADCs to create novel ADCs. ADC Therapeutics entered into the ADCT Collaboration Agreement with us to evaluate the use of our SAFEbody technology with respect to up to two exclusive targets selected by ADC Therapeutics. Upon our delivery of certain initial results, ADC Therapeutics has the option to license our SAFEbody technology with respect to one or both targets as further detailed below. ADC Therapeutics has not yet exercised such options as of the date of this annual report.

Both parties are required to use commercially reasonable efforts to perform certain development obligations under the ADCT Collaboration Agreement. Additionally, we are subject to exclusivity obligations to ADC Therapeutics under the ADCT Collaboration Agreement with respect to (i) the targets for which ADC Therapeutics has a license or an option to license and (ii) the use or licensing of our intellectual property that is necessary or useful to the development plan under the ADCT Collaboration Agreement or that would preclude us from granting to ADC Therapeutics the licenses under the ADCT License Agreement. ADC Therapeutics owns intellectual property that are specific to the SAFEbodies that we develop under the ADCT Collaboration Agreement with respect to the two elected targets, and we will own all intellectual property developed under the ADCT Collaboration Agreement that relates generally to our SAFEbody platform.

Under the ADCT Collaboration Agreement, we are eligible to receive up to US$1,600,000 in consideration for our exclusivity obligations, upon achievement of certain development milestones and upon ADC Therapeutics' election to proceed with development for the two elected targets. As of the date of this annual report, we have received US$550,000 in aggregate payments under the ADCT Collaboration Agreement. ADC Therapeutics has the right to terminate the ADCT Collaboration Agreement at any time and for any reason in its entirety or on a target-by-target basis upon thirty days' prior written notice to us. Either party may terminate the ADCT Collaboration Agreement, in its entirety or on a target-by-target basis, upon the other party's uncured material breach of the agreement or the other party's insolvency-related events.

ADCT License Agreement

Subject to the exercise of the options contained in the ADCT Collaboration Agreement, we have granted ADC Therapeutics, with respect to each elected target, an exclusive, worldwide, perpetual and irrevocable (subject only to the termination provisions) license (with the right to grant sublicenses) to develop, make, use, commercialize and import the antibody drug conjugates that comprise masked antibodies generated by us under these programs. Subject to certain conditions, including the exercise by ADC Therapeutics of its first option to license our SAFEbody technology, ADC Therapeutics will grant us the option to negotiate a license to develop, manufacture and commercialize ADCs containing our SAFEbody technology in Greater China.

Under the ADCT License Agreement, if ADC Therapeutics exercises both of its options granted thereunder, we could be eligible to receive up to US$166,090,000 in aggregate milestone payments, in addition to mid-single-digit percentage net sales-based tiered royalties on products licensed under the ADCT License Agreement, subject to certain reductions. Royalties, if any, will be payable on a country-by-country and product-by-product basis, until the earlier of (i) the tenth anniversary of the first commercial sale of such product or (ii) the expiration of the last-to-expire patent licensed under the agreement in such country, unless earlier terminated by the parties, following which any licenses granted to ADC Therapeutics under the ADCT License Agreement shall become fully paid up, perpetual and irrevocable. In addition to the contingent milestone and royalty payments, if ADC Therapeutics exercises both of its options granted under the ADCT Collaboration Agreement, we are also entitled to a mid-six-figure dollar amount annual maintenance fee. ADC Therapeutics has not yet exercised the options contained in the ADCT Collaboration Agreement as of the date of this annual report. Therefore, we have not received any payment under the ADCT License Agreement.

ADC Therapeutics has the right to terminate the ADCT License Agreement before the expiration of the royalty term on a product-by-product basis or in its entirety (i) for any reason or no reason upon thirty days' written notice to us, or (ii) if ADC Therapeutics chooses to discontinue the development or sale of the applicable licensed product worldwide. Each party has certain rights to terminate the ADCT License Agreement with prior written notice upon the other party's uncured material breach or insolvency.

Sanjin Collaboration/ Out-Licensing Agreements

2018 Collaboration Agreements

In December 2018, we entered into (i) a collaboration agreement (the "Sanjin Greater China Agreement") that covers Greater China with Guilin Sanjin Pharmaceutical Co., Ltd. ("Sanjin") and certain of its subsidiaries (collectively, "Sanjin Parties") and (ii) a collaboration agreement (the "Sanjin ROW Agreement," together with the Sanjin Greater China Agreement, the "2018 Sanjin Agreements") that covers the regions other than Greater China with Sanjin. Pursuant to the Sanjin Greater China Agreement, we transferred the Chinese intellectual property directly related to a monoclonal antibody molecule that binds to the PD-L1 target (the "PD-L1 Project"), including patent rights, patent application rights and technologies based on the core sequence of the molecule, to Sanjin Parties. Sanjin Parties will own all the Chinese intellectual property developed in the exercise of Sanjin Parties' rights under the agreement, including but not limited to improvements (including combination products), clinical trials, regulatory filings, and commercialization rights relating thereto. We also granted Sanjin Parties a royalty-free license to use our other existing intellectual property and improvements thereto which are related to the PD-L1 Project for the purposes of exploiting its rights and performing its obligations under the agreement. Sanjin Parties will enjoy all the economic benefits deriving from the PD-L1 Project in Greater China, including but not limited to patent transfer fee, licensing fee, sales revenue and sales commission, etc. Sanjin Parties will pay us (i) within the validity period of the patent of PD-L1 molecule, single-digit percentage of net sales of the products that use the licensed antibody after such products enter the market and (ii) a low to mid-low double-digit percentage of the profits resulting from any transfer of the license to any third parties depending on the timing of the transfer relative to the development stage of the product. We also received a low-seven figure dollar upfront fee upon the effectiveness of the agreement from Sanjin Parties.

Pursuant to the Sanjin ROW Agreement, we granted Sanjin a royalty-free license to use all intellectual property relating to (i) the collaboration under the agreement that we controlled before we entered into the agreement or acquired independently of the agreement and (ii) improvements thereto for the purposes of exploiting its rights and performing its obligations under the agreement. Any intellectual property generated independently by a party under the agreement will be solely owned by that party who generated such intellectual property, and any intellectual property generated from cooperation between us and Sanjin's affiliates in connection with the collaboration will be jointly owned. We have the right to apply for the patents derived from our core and key technologies pertaining to the PD-L1 molecule in the rest of the world and we retain a majority of the economic benefits derived from the Sanjin ROW Agreement, including but not limited to any patent transfer fee, licensing fee and gains realized under such transfer. In case we intend to transfer to a third party our share of economic interests in any country outside of Greater China, we must notify Sanjin and Sanjin will receive a right of first refusal if it pays us a deposit equal to a low double-digit percentage of the consideration that we expect to receive from such third party. If Sanjin waives the right of first refusal, we can proceed with the transfer, provided that the final transaction price with the third party is not lower than the amount of the offering price that was included in our notice to Sanjin.

Under the 2018 Sanjin Agreements, we agreed not to (i) independently develop any monospecific antibodies that bind to the PD-L1 target or (ii) grant any rights associated with such antibodies to any third parties during the three-year period from the effective date of the agreements. The exclusivity obligation does not prevent us from (i) developing or granting any licenses to third parties for intellectual property that covers bispecific antibodies, ADCs, diagnostic antibodies, nano-particles and probody against PD-L1 target and (ii) continuing to provide antibody screening service that were commenced before the execution of the Sanjin Greater China Agreement and either party has the independent right to conduct combination therapy studies outside of the Greater China. Either non-breaching party may terminate the 2018 Sanjin Agreements if the other party's ability to comply with its respective obligations under the agreements is negatively affected by contingencies such as failure to maintain operation or changes in core project management and the other party fails to take effective remedial measures. Each agreement automatically terminates upon the termination of the other agreement. Upon the rescission or termination, Sanjin Parties will return to us all the intellectual property transferred by us to the Sanjin Parties as well as documents and data provided by us under the 2018 Sanjin Agreements. The 2018 Sanjin Agreements are governed by PRC law.

During 2021, Sanjin advanced this anti-PDL-1 monoclonal antibody (ADG104) into Phase 2 development, following completion of a Phase 1 program that, according to Sanjin, showed an ORR in NPC of over 30%. Clinical development of this candidate is ongoing.

2019 Collaboration Agreements

In May 2019, we entered into (i) a collaboration agreement that covers Greater China (the "Dragon Boat Greater China Agreement") and (ii) a collaboration agreement that covers the regions other than Greater China (the "Dragon Boat ROW Agreement," together with the Dragon Boat Greater China Agreement, the "2019 Dragon Boat Agreements"), with Dragon Boat Biopharmaceutical (Shanghai) Limited. ("Dragon Boat"), a subsidiary of Sanjin. Pursuant to the Dragon Boat Greater China Agreement, we will transfer the Chinese intellectual property directly related to a certain monoclonal antibody molecule (the "Specified Molecule") that binds to a specified target (the "Specified Project"), including the patent rights, patent application rights and technologies based on the core sequence of the molecule, to Dragon Boat. Dragon Boat will own all the Chinese intellectual property developed in the exercise of Dragon Boat's rights under the agreement, including but not limited to improvements (including combination products), clinical trials, regulatory filings, and commercialization rights relating thereto. We also granted Dragon Boat a royalty-free license to use our other existing intellectual property and improvements thereto which are related to the Specified Project for the purposes of exploiting its rights and performing its obligations under the agreement. Dragon Boat will enjoy all the economic benefits deriving from the Specified Project in Greater China, including but not limited to patent transfer fee, licensing fee, sales revenue and sales commission, etc. and will pay us (i) RMB6,000,000 (equivalent to approximately US$0.9 million) milestone payments and (ii) a single-digit percentage of net sales of the products that within the validity period of the patent of the Specified Molecule use the licensed antibody after such products enter the market. Dragon Boat also paid us a mid-six figure dollar upfront fee upon the signing of the agreement.

Pursuant to the Dragon Boat ROW Agreement, we granted Dragon Boat a royalty-free license to use all intellectual property relating to (i) the collaboration under the agreement that we controlled before we entered into the agreement or acquired independently of the agreement and (ii) improvements thereto for the purposes of exploiting its rights and performing its obligations under the agreement. Any intellectual property generated independently by a party under the agreement will be solely owned by that party who generated such intellectual property, and any intellectual property generated from cooperation between us and Dragon Boat in connection with the collaboration will be jointly owned. We have the right to apply for the patents derived from our core and key technologies pertaining to the Specified Molecule in the rest of the world and we retain a majority of the economic benefits derived from the Dragon Boat ROW Agreement, including but not limited to any patent transfer fee, licensing fee and gains realized under such transfer. In case we intend to transfer to a third party our share of economic interests in any country outside of Greater China, we must notify Dragon Boat and Dragon Boat will receive a right of first refusal if it pays us a deposit equal to a low double-digit percentage of the consideration that we expect to receive from such third party. If Dragon Boat waives the right of first refusal, we can proceed with the transfer, provided that the final transaction price with the third party is not lower than the amount of the offering price that was included in our notice to Dragon Boat.

Under the 2019 Dragon Boat Agreements, we agreed not to (i) independently develop any monospecific antibodies that bind to the specified target or (ii) grant any rights associated with such antibodies to any third parties during the three-year period from the effective date of the agreements. The exclusivity obligation does not prevent us from (i) developing or granting any licenses to third parties for intellectual property that covers bispecific antibodies, ADCs, diagnostic antibodies, nano-particles and probody against the specific target and (ii) continuing to provide antibody screening service that were commenced before the execution of the Dragon Boat Greater China Agreement and either party has the independent right to conduct combination therapy studies outside of the Greater China. Either nonbreaching party may terminate the 2019 Dragon Boat Agreements if the other party's ability to comply with its obligations under the agreements is negatively affected by contingencies such as failure to maintain operation or changes in core project management and the other party fails to take effective remedial measures. Each agreement automatically terminates upon the termination of the other agreement. Upon the rescission or termination, Dragon Boat will return to us all the intellectual property transferred by us to Dragon Boat as well as documents and data provided by us under the 2019 Dragon Boat Agreements. The 2019 Dragon Boat Agreements are governed by PRC law.

During 2021, Dragon Boat advanced this candidate, an anti-CSF-1R monoclonal antibody (ADG125/BC006) into phase 1 development. Clinical development of this candidate is ongoing.

As of the date of this annual report, we have received approximately US$1.5 million and US$1.2 million in aggregate payments under the 2018 Sanjin Agreements and the 2019 Dragon Boat Agreements, respectively.

ADDITIONAL DISCOVERY AGREEMENTS

In addition to our SAFEbody technology licensing collaborations and out-licensing collaborations, from time to time, we further enhance our discovery efforts to leverage our DPL platform and antibody engineering capabilities with other biotechnology and pharmaceutical companies. These activities further validate our technologies and establish foundations to expand our relationships with various organizations and global biopharmaceutical companies with whom we may partner in the future.

Examples of such prior agreements include:

- We collaborated with Dr. Richard Childs, Chief of the Laboratory of Transplantation Immunotherapy at National Heart Lung and Blood Institute, part of the National Institutes of Health, or NIH, NHLBI, who has used antibodies discovered by us to develop a CAR-T cell therapy candidate targeting a human endogenous retrovirus expressed in the majority of clear cell kidney tumors. In January 2021, we announced the successful completion of our component of the collaboration. The NIH now leads and is responsible for the manufacturing and clinical development of the CAR-T cell therapy candidate.

- Under a material transfer agreement, we developed SAFEbody drug conjugates candidates against a tumor target selected by Tanabe Research Laboratories, Inc.

- We had worked with Celgene (now Bristol-Myers Squibb) to discover antibodies targeting novel antigens using our proprietary DPL platform.

- We collaborated with GlaxoSmithKline (China), or GSK China, where we were engaged to generate high affinity antibodies against multiple epitopes of multi-transmembrane targets; and

- We worked with Jiangsu Hengrui Medicine Company Limited, or Jiangsu Hengrui, where we were able to discover cross-reactive agonistic antibody for immuno-oncology.

INTELLECTUAL PROPERTY

Protection of our intellectual property is fundamental to the long-term success of our business. Specifically, our success is dependent on our ability to obtain and maintain protection for our technology and the know-how related to our business, defend and enforce our intellectual property rights, and operate our business without infringing, misappropriating, or otherwise violating valid and enforceable intellectual property rights of others. Our patent strategy is focused on seeking coverage for our core technologies and products, such as the DPL platform, ADG116, ADG126, ADG106 and ADG206. We also rely on trade secret protection of our confidential information and know-how relating to our proprietary technology, platforms and product candidates, and continuing innovation to develop, strengthen, and maintain our proprietary position in our technology, platforms and product candidates. We expect to rely on data exclusivity, market exclusivity, patent term adjustment and patent term extensions when available.

As of March 31, 2023, we owned three issued patents and nine pending patent applications in China and we also owned two issued patents and ten pending applications in Europe filed with the European Patent Office, five issued patents, 16 pending patent applications and four pending provisional applications in the United States, as well as 11 pending international PCT applications, three issued patents and 90 pending patent applications in other jurisdictions. Our patents and patent applications cover our key technologies and product candidates, including the DPL platform, our clinical candidates, ADG116, ADG126, ADG106, ADG206 and our preclinical candidates including ADG153, ADG138 and ADG152. Excluding any patent term adjustment and patent term extension, our currently issued patents are expected to expire from 2033 to 2038. If any patents issue from our pending patent applications, excluding any patent term adjustments and patent term extension, such patents will be expected to expire from 2033 to 2043. If any patents issue from our pending patent applications, excluding any patent term adjustments and patent term extension, such patents will be expected to expire from 2033 to 2042. The following table summarizes material pending patent applications in the United States, China, Europe and under Patent Cooperation Treaty, or PCT, covering our product candidates, including ADG116, ADG126, ADG106 and ADG104 and ADG125.

Product Candidates	Title of Patent Application	Type of Patent Applications(1)	Jurisdiction
ADG116	Anti-CTLA4 antibodies and methods of making and using the same	Composition of matter/ method of use/ method of making	United States of America, China and European Patent Office
ADG126	Anti-CTLA4 antibodies and methods of making and using the same	Composition of matter/ method of use/ method of making	United States of America, China and European Patent Office
ADG106	Anti-CD137 molecules and uses thereof Combination therapy comprising anti-CD137 antibodies	Composition of matter/ method of use/ method of making method of treatment/ method of use	United States of America China and European Patent Office
ADG206	Anti-CD137 antibodies and methods of making and using the same	Composition of matter/method of use/method of making	Patent Cooperation Treaty(2)
ADG104	Anti-PD-L1 antibodies and use thereof	Composition of matter/ method of use/ method of making	United States of America and European Patent Office
ADG125	Anti-CSF1R molecules and use thereof	Composition of matter/method of use/method of making	United States of America and European Patent Office

(1) You should read the Risk Factors included elsewhere in this annual report for important information about risks posed by the loss of patent protection, in particular the risks described under “Item 3 Key Information—3.D.Risk Factors—Risks Related to Our Intellectual Property.”

(2) Patent Application of ADG125 has not yet entered into national phase of Patent Cooperation Treaty.

The following table summarizes material issued patents in Europe and China covering our proprietary technologies and product candidates.

Application No.	Title of Patent	Type of Patent(1)	Jurisdiction
13877452.6	An Integrated System for Library Construction, Affinity Binder Screening and Expression Thereof	Method	European Patent Office
201380074656.1	An Integrated System for Library Construction, Affinity Binder Screening and Expression Thereof	Method	China
14908246.3	Methods and Systems for Autoinduction of Protein Expression	Method	European Patent Office
201410789857.6	Filter Vector System And Its Applications	Method	China
16108018	Anti-CD137 Molecules and Use Thereof	Composition of matter	United States of America
15536939	Methods and Systems for Autoinduction of Protein Expression	Method	United States of America
201480084652.6	Methods and Systems for Autoinduction of Protein Expression	Method	China
16640673	Dynamic Human Antibody Light Chain Libraries	Library	United States of America
16640679	Dynamic Human Heavy Chain Antibody Libraries	Library	United States of America
16265946	Anti-CTLA4 Antibodies And Methods of Making and Using the Same	Composition of matter	United States of America

(1) You should read the Risk Factors included elsewhere in this annual report for important information about risks posed by the loss of patent protection, in particular the risks described under “Item 3 Key Information—3.D.Risk Factors—Risks Related to Our Intellectual Property.”

We continually assess and refine our intellectual property strategy as we develop new platform technologies and product candidates. To that end, we are prepared to file additional patent applications relating to the new technologies that we develop if our intellectual property strategy requires such filings, or where we seek to adapt to competition or seize business opportunities. In addition to filing and prosecuting patent applications in China and the United States, we may elect to file counterpart patent applications in additional countries and regions where we believe such foreign filing is likely to be beneficial.

As with other biotechnology and biopharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our platform technologies and product candidates will depend on our success in obtaining effective patent claims and enforcing those claims if granted. However, our owned pending patent applications, and any patent applications that we may in the future file or license from third parties may not result in the issuance of patents. In addition, the term of individual issued patents depends upon the legal term for patents in the countries in which they are obtained. In most countries in which we have filed or intend to file in the future, including the United States, the patent term is 20 years from the earliest filing date of a nonprovisional patent application. We intend to seek patent term extensions to any of our issued patents in any jurisdiction where these are available; however, there is no guarantee that the applicable authorities will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions. The life of a patent, and the protection it affords, is therefore limited and once the patent life of our issued patents has expired, we may face competition, including from other competing technologies. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

We seek to ensure that investments made into the development of our technology are protected by relying on a combination of patents, trademarks, copyrights, trade secrets and contractual rights, including license agreements. In addition to our patent portfolio described above, as of March 31, 2023, our PRC subsidiary owned 62 registered trademarks relating to various aspects of our operations, and two registered domain names in China. To protect our rights, we seek to enter into confidentiality agreements, nondisclosure agreements and employee disclosure and invention assignment agreements with our employees, contractors and other third parties who may have or need access to our confidential information. We have also employed internal policies, encryptions and data security measures to protect our proprietary rights. However, there can be no assurance that our efforts will be successful. If our employees, contractors or other third parties violate these agreements or otherwise infringe upon, misappropriate or otherwise violate our intellectual property rights, we may seek to enforce our rights against such parties. In addition, from time to time, third parties may initiate litigation against us alleging infringement, misappropriation or other violation of their proprietary rights or declaring their noninfringement of our intellectual property rights. An adverse result in any such proceeding could enjoin the commercialization of our technology platform and product candidates, result in significant damages, and have a material adverse effect on our business. Even if we are successful in any such litigation, we may be required to incur significant costs and dedicate significant personnel time in defending such litigation. For more information on these and other risks related to intellectual property, see “Item 3 Key Information —3.D. Risk Factors—Risks Related to Our Intellectual Property.”

MANUFACTURING AND SUPPLY

Adagene currently outsources the GMP manufacturing, QC testing and QA release of clinical trial materials to WuXi Biologics. We have entered into a framework agreement with Wuxi Biologics, under which it provides services to us on a project-by-project basis. Adagene is also working with other qualified manufacturers to diversify manufacturing outsourcing for the clinical supply production. Adagene has assembled a seasoned internal team with rich experience to oversee the clinical manufacturing to comply with cGMP guidelines and other applicable regulations required by agencies. Currently, Wuxi Biologics as our main CDMO is responsible for obtaining raw materials from multiple suppliers that we believe have sufficient capacity to meet our demands. We expect to continue our relationships with WuXi Biologics while Adagene is continuously evaluating multiple global vendors to ensure continuous supply of Adagene pipeline products for on-going and planned clinical trials.

COMPETITION

The biotechnology and pharmaceutical industries are highly competitive and characterized by continuing technological advancement, significant competition and an emphasis on intellectual property. While we believe that our management’s research, development and commercialization experience provide us with competitive advantages, we face potential competition from many different sources, including global biopharmaceutical companies, major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies, universities, academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for the research, development, manufacturing and commercialization of cancer immunotherapies. Any product candidates that we successfully develop and commercialize will compete with new immunotherapies and other drug products that may become available in the future. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer and more effective, have fewer or less severe side effects or are more convenient than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we do.

We compete in the segments of the pharmaceutical, biotechnology and other related markets that develop cancer treatments. There are many other companies that have commercialized and/or are developing immuno-oncology treatments for cancer, including large pharmaceutical and biotechnology companies. Many of our competitors have significantly greater financial, technical and human resources than we have, and mergers and acquisitions in the biopharmaceutical industry may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. Our commercial opportunities could be reduced or eliminated if our competitors develop or market products or other novel therapies that are more effective, safer or less costly than our current or future product candidates, or obtain regulatory approval for their products more rapidly than we may obtain approval for our product candidates.

Our clinical stage products include ADG116 and ADG126, which are investigational fully human anti-CTLA-4 mAbs generated through our NEObody and SAFEbody technologies, respectively. We expect our primary competition for these two candidates to be within the anti-CTLA-4 antibody market. As of March 31, 2023, Yervoy (ipilimumab) from BMS and Imjudo (tremelimumab) from AstraZeneca are the two marketed anti-CTLA-4 therapies approved by FDA for various cancer indications. Iplilimumab is approved both as a monotherapy and a combination therapy in six indications, while tremelimumab is approved as a combination therapy for two indications.

In addition to the marketed anti-CTLA-4 therapies, there are multiple “next generation” anti-CTLA-4 antibodies in clinical development globally. Examples of these programs include: Agenus (Zalifrelimab/AGEN1181), Bristol-Myers Squibb Company (BMS-986249, BMS-986288), Merck (quavonlimab/MA-1308), Onco-C4, Inc. (ONC-392) and Xilio (XTX101). Yervoy was also approved in China in 2021, where additional CTLA-4 antibodies are in clinical development. These anti-CTLA-4 therapies in development in China include HBM4003 from Harbour BioMed and CD1002 from CStone Pharmaceuticals (Suzhou) Co., Ltd.

Major limitations of anti-CTLA-4 mAbs include toxicity. According to our internal market analysis, nivolumab and ipilimumab combination therapy has shown relatively higher toxicity in clinical studies even at lower dosages, which was observed from the published clinical data. We believe that the continued expansion of indications, and the launch of innovative novel anti-CTLA-4 antibodies with potential for higher safety and better efficacy may increase the market for CTLA-4 antibodies significantly.

We are also developing the anti-CD137 targeting antibodies ADG106 and ADG206. We expect our primary competition for this candidate to be with other clinical-stage CD137 agonist product candidates. As of the date of this annual report, there are no marketed CD137 agonist drugs. The two leading molecules in clinical trials are utomilumab (PF-05082566) from Pfizer and urelumab (BMS-663513) from BMS. Other anti-CD137 candidates in earlier stages of development include ATOR-1017 from Alligator Bioscience, CTX-471 from Compass, and AGEN2373 from Agenus.

INSURANCE

We provide social security insurance including pension insurance, unemployment insurance, work-related injury insurance and medical insurance for our employees. We maintain property insurance, general liability insurance, products/completed operations insurance, auto and international auto liability insurance, workers compensation insurance, key-men insurance, international workers compensation insurance, accident and health insurance and director and officer liabilities insurance. We consider our insurance coverage sufficient and in line with market practice for our business operations in the industry.

LEGAL PROCEEDINGS

From time to time, we may become involved in legal proceedings or be subject to claims arising in the ordinary course of our business. As of the date of this annual report, we are not presently a party to any legal proceedings that, if determined adversely to us, would individually or taken together have a material adverse effect on our business, results of operations, financial condition or cash flows. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

MATERIAL LICENSES AND APPROVALS

The following table sets forth a list of material licenses and approvals, subject to further renewal, that our PRC subsidiary is required to obtain to carry out our operations in China.

License	Entity Holding the License	Regulatory Authority
Business License	Adagene Suzhou	SAMR
Approval Letter for Drug Clinical Trial of ADG104*	Adagene Suzhou	NMPA
Approval Letter for Drug Clinical Trial of ADG106	Adagene Suzhou	NMPA
Approval Letter for Drug Clinical Trial of ADG116	Adagene Suzhou	NMPA
Approval Letter for Drug Clinical Trial of ADG126	Adagene Suzhou	NMPA

* Note: We have out-licensed the Greater China rights of ADG104 to our partner Sanjin.

REGULATION

United States Regulation

The FDA and other regulatory authorities at federal, state, and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, safety, effectiveness, labeling, packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring and post-approval reporting of biologics such as those we are developing. We, along with third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates.

In the United States, the FDA regulates biologic products under the Federal Food, Drug and Cosmetic Act, and the Public Health Service Act and the implementing regulations and other laws, including, in the case of biologics, the Public Health Service Act. Our product candidates are subject to regulation by the FDA as biologics. Biologics require the submission of a BLA and licensure, which constitutes approval, by the FDA before being marketed in the United States. None of our product candidates has been approved by the FDA for marketing in the United States, and we currently have no BLAs pending. Failure to comply with applicable FDA or other requirements at any time during product development, clinical testing, the approval process or after approval may result in administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, suspension or revocation of approved applications, warning letters, product recalls, product seizures, total or partial suspensions of manufacturing or distribution, injunctions, fines, civil penalties or criminal prosecution.

The process required by the FDA before biologic product candidates may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests and animal studies performed in accordance with the FDA's GLP regulations;
- submission to the FDA of an IND, which must become effective before clinical trials may begin and must be updated annually or when significant changes are made;
- approval by an independent Institutional Review Board, or IRB, or ethics committee at each clinical site before the trial is commenced;
- performance of adequate and well-controlled human clinical trials to establish the safety and effectiveness of the proposed biologic product candidate for its intended indications;

- preparation of and submission to the FDA of a BLA when adequate data are obtained from pivotal clinical trials;
- a determination by the FDA within 60 days of its receipt of a BLA to accept the application for review;
- satisfactory completion of an FDA Advisory Committee review, if applicable;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the proposed product is produced to assess compliance with cGMP and to assure that the facilities, methods and controls are adequate to preserve the biological product's continued safety, purity and potency, and of selected clinical investigation sites to assess compliance with Good Clinical Practices, or GCP regulations; and
- FDA review and approval of the BLA to permit commercial marketing of the product for particular indications for use in the United States.

Preclinical and Clinical Development

Prior to beginning the first clinical trial with a product candidate in the United States, we must submit an IND application to the FDA. An IND application is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND application is on the general investigational plan and the protocol(s) for clinical trials. The IND application also includes results of animal and in vitro studies assessing the toxicology, pharmacokinetics, pharmacology, and pharmacodynamic characteristics of the product; chemistry, manufacturing, and controls information; and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises safety concerns or questions about the proposed clinical trial. If the IND sponsor is not able to address FDA's concerns satisfactorily within the 30-day time frame, the IND may be placed on clinical hold. The IND sponsor and the FDA must resolve any outstanding concerns or questions before the IND is cleared by the FDA and the clinical trial can begin. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Generally, a separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. Furthermore, an independent IRB for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site, and must monitor the study until completed. Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies also include oversight by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board, or DSMB, which provides recommendation on whether or not a study should move forward at designated check points based on access to certain data from the study. The DSMB may recommend halting of the clinical trial if it determines that there is an unacceptable safety risk for subjects or on other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing clinical trials and clinical trial results to public registries.

For purposes of BLA approval, human clinical trials are typically conducted in three sequential phases that may overlap.

- Phase I—The investigational product is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. For investigational products developed for oncology indications, the Phase I trials are normally conducted in patients with serious or life-threatening diseases without other treatment alternatives.

- Phase II—The investigational product is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks. Multiple Phase II clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase III clinical trials. For certain indications in patients with serious or life-threatening diseases and with no available therapies, it may be possible to obtain BLA approval based on data from Phase II trials if a positive benefit risk profile is demonstrated.

- Phase III—The investigational product is administered to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval.

In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so-called Phase 4 studies may be made a condition to approval of the BLA. Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the biological characteristics of the product candidate, and must finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product, or for biologics, the safety, purity and potency. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

BLA Submission and Review

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, preclinical studies and clinical trials are submitted to the FDA as part of a BLA requesting approval to market the product for one or more indications. The BLA must include all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. The submission of a BLA requires payment of a substantial application user fee to the FDA unless a waiver or exemption applies.

Once an original BLA has been submitted, FDA has 60 days to determine whether the application can be filed. If FDA determines that an application to be deficient, on its face, in a way that precludes a complete review, FDA may not accept the application for review and may issue a refuse-to-file letter to the sponsor. If FDA determines the application is filable, the FDA's goal is to review standard applications within ten months after it accepts the application for filing, or, if the application qualifies for priority review, six months after the FDA accepts the application for filing. In both standard and priority reviews, the review process is often significantly extended by FDA requests for additional information or clarification. The FDA reviews a BLA to determine, among other things, whether a product is safe, pure and potent and the facilities in which it is manufactured, processed, packed, or held meets standards designed to assure the product's continued safety, purity and potency. The FDA may convene an advisory committee to provide clinical insight on application review questions. Before approving a BLA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates a BLA and conducts inspections of manufacturing facilities where the commercial product and/or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A Complete Response letter will describe all of the deficiencies that the FDA has identified in the BLA, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the Complete Response letter without first conducting required inspections, testing submitted product lots, and/or reviewing proposed labeling. In issuing the Complete Response letter, the FDA may recommend actions that the applicant might take to place the BLA in condition for approval, including requests for additional information or clarification. The FDA may delay or refuse approval of a BLA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the BLA with a Risk Evaluation and Mitigation Strategy, or REMS, to ensure the benefits of the product outweigh its risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a product and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing requirements is not maintained or if problems occur after the product reaches the marketplace. The FDA may require one or more Phase 4 post-market studies and surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies.

Expedited Development and Review Programs

The FDA offers a number of expedited development and review programs for qualifying product candidates. The fast track program is intended to expedite or facilitate the process for reviewing new products that meet certain criteria. Specifically, new products are eligible for fast track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a fast track product has opportunities for frequent interactions with the review team during product development and, once a BLA is submitted, the product may be eligible for priority review. A fast track product may also be eligible for rolling review, in which case the FDA may consider for review sections of the BLA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the BLA, the FDA agrees to accept sections of the BLA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the BLA.

A product intended to treat a serious or life-threatening disease or condition may also be eligible for breakthrough therapy designation to expedite its development and review. A product can receive breakthrough therapy designation if preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the fast track program features, as well as more intensive FDA interaction and guidance beginning as early as Phase I and an organizational commitment to expedite the development and review of the product, including involvement of senior managers.

Any marketing application for a biologic submitted to the FDA for approval, including a product with a fast track designation and/or breakthrough therapy designation, may be eligible for other types of FDA programs intended to expedite the FDA review and approval process, such as priority review and accelerated approval. A product is eligible for priority review if it has the potential to provide a significant improvement in the treatment, diagnosis or prevention of a serious disease or condition compared to marketed products. For products containing new molecular entities, priority review designation means the FDA's goal is to take action on the marketing application within six months of the 60-day filing date (compared with ten months under standard review).

Additionally, products studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA will generally require the sponsor to perform adequate and well- controlled post-marketing clinical trials to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

In 2017, FDA established a new regenerative medicine advanced therapy, or RMAT, designation as part of its implementation of the 21st Century Cures Act, which was signed into law in December 2016. The RMAT designation program is intended to fulfill the 21st Century Cures Act requirement that FDA facilitate an efficient development program for, and expedite review of, any drug that meets the following criteria: (1) it qualifies as a RMAT, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions; (2) it is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and (3) preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition. Like fast track and breakthrough therapy designation, RMAT designation provides potential benefits that include more frequent meetings with the FDA to discuss the development plan for the product candidate and eligibility for rolling review and priority review. Products granted RMAT designation may also be eligible for accelerated approval on the basis of a surrogate or intermediate endpoint reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites. Once approved, when appropriate, the FDA can permit fulfillment of post-approval requirements under accelerated approval through the submission of clinical evidence, clinical trials, patient registries, or other sources of real-world evidence such as electronic health records; through the collection of larger confirmatory datasets; or through post-approval monitoring of all patients treated with the therapy prior to approval.

Fast track designation, breakthrough therapy designation, priority review, accelerated approval, and RMAT designation do not change the standards for approval but may expedite the development or approval process.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making available a drug or biologic for this type of disease or condition will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting a BLA. After the FDA grants orphan drug designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. The orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review or approval process.

If a product that has orphan drug designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusive approval (or exclusivity), which means that the FDA may not approve any other applications, including a full BLA, to market the same biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the BLA application fee.

A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Post-Approval Requirements

Any products manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing user fee requirements, under which FDA assesses an annual program fee for each product identified in an approved BLA. Biologic manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP, which impose certain procedural and documentation requirements upon us and our third-party manufacturers. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of a product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of existing product approvals;
- product seizure or detention, or refusal of the FDA to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA closely regulates the marketing, labeling, advertising and promotion of biologics. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product’s labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer’s communications on the subject of off-label use of their products.

Biosimilars and Reference Product Exclusivity

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the ACA, signed into law in 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA, which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-approved reference biological product.

Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical trial or studies. Interchangeability requires that a product be biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product in any given patient and, for products that are administered to a patient more than once, the biologic and the reference biologic may be alternated or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. Complexities associated with the larger, and often more complex, structures of biological products, as well as the processes by which such products are manufactured, pose significant hurdles to implementation of the abbreviated approval pathway that are still being worked out by the FDA.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the FDA may not approve a biosimilar product until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA containing that applicant's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of the competing product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, FDA has stated that products deemed "interchangeable" can be readily substituted by pharmacies, depending on state pharmacy laws.

The BPCIA is complex and continues to be interpreted and implemented by the FDA. In addition, government proposals have sought to reduce the 12-year reference product exclusivity period. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. As a result, the ultimate implementation and impact of the BPCIA is subject to significant uncertainty.

Other Healthcare Laws and Compliance Requirements

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business. Such laws include, without limitation:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, receiving, offering or paying remuneration, to induce, or in return for, either the referral of an individual, or the purchase or recommendation of an item or service for which payment may be made under any federal healthcare program;

- federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment to the federal government, including federal healthcare programs, that are false or fraudulent;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes which prohibit, among other things, executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters, and which, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, also imposes certain requirements on HIPAA covered entities and their business associates relating to the privacy, security and transmission of individually identifiable health information;

- the U.S. federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to annually report to the federal government, information related to payments or other transfers of value made to physicians, as defined by such law, certain other health care providers beginning in 2022, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

- United States state and foreign law equivalents of each of the above federal laws, which, in some cases, differ from each other in significant ways, and may not have the same effect, thus complicating compliance efforts, including laws governing the privacy and security of personal data, such as the GDPR, which imposes obligations and restrictions on the collection and use of personal data relating to individuals located in the EU and EEA (including with regard to health data).

If their operations are found to be in violation of any of such laws or any other governmental regulations that apply, they may be subject to significant penalties, including, without limitation, civil, criminal and administrative penalties, damages, fines, exclusion from government-funded healthcare programs, such as Medicare and Medicaid or similar programs in other countries or jurisdictions, integrity oversight and reporting obligations to resolve allegations of non-compliance, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any pharmaceutical or biological product for which we obtain regulatory approval. Sales of any product depend, in part, on the extent to which such product will be covered by third-party payers, such as federal, state, and foreign government healthcare programs, commercial insurance and managed healthcare organizations, and the level of reimbursement for such product by third-party payers. Decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. As there is no uniform policy of coverage and reimbursement for drug products among third-party payers in the United States, coverage and reimbursement policies for drug products can differ significantly from payer to payer. There may be significant delays in obtaining coverage and reimbursement as the process of determining coverage and reimbursement is often time-consuming and costly which will require us to provide scientific and clinical support for the use of our products to each payer separately, with no assurance that coverage or adequate reimbursement will be obtained. It is difficult to predict at this time what government authorities and third-party payers will decide with respect to coverage and reimbursement for our drug products. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization.

In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Third-party payers are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost effectiveness of pharmaceutical or biological products, medical devices and medical services, in addition to questioning safety and efficacy. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit sales of any product. Decreases in third-party reimbursement for any product or a decision by a third-party payer not to cover a product could reduce physician usage and patient demand for the product.

Healthcare Reform

The United States and some foreign jurisdictions are considering or have enacted a number of reform proposals to change the healthcare system. There is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by federal and state legislative initiatives, including those designed to limit the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded healthcare programs, and increased governmental control of drug pricing.

In March 2010, the ACA was signed into law, which substantially changed the way healthcare is financed by both governmental and private insurers in the United States, and significantly affected the pharmaceutical industry. The ACA contains a number of provisions of particular import to the pharmaceutical and biotechnology industries, including, but not limited to, those governing enrollment in federal healthcare programs, a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, and annual fees based on pharmaceutical companies' share of sales to federal healthcare programs.

Since its enactment, there have been judicial, Congressional, and executive branch challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. For example, the 2020 federal spending package permanently eliminates, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. In addition, the Tax Act was enacted, which, among other things, removes penalties for not complying with ACA's individual mandate to carry health insurance. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas ruled that the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. On March 2, 2020, the U.S. Supreme Court granted the petitions for writs of certiorari to review this case, although it is unclear when or how the Supreme Court will rule. It is also unclear how other efforts to challenge, repeal or replace the ACA will impact the ACA.

Other legislative changes have been proposed and adopted since the ACA was enacted, including aggregate reductions of Medicare payments to providers of 2% per fiscal year and reduced payments to several types of Medicare providers, which will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through December 31, 2020, unless additional Congressional action is taken. Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products.

At the federal level, the Trump administration's budget proposal for fiscal year 2021 includes a US$135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. Further, the Trump administration released a "Blueprint," or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out- of-pocket costs of drug products paid by consumers. The Department of Health and Human Services, or HHS, has solicited feedback on some of these measures and has implemented others under its existing authority. For example, in May 2019, the Centers for Medicare & Medicaid Services, or CMS, issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. Most recently, in July 2020, President Trump also signed a number of executive orders that attempt to implement several of the Administration's proposals. While some of measures may require additional authorization to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. We expect that these and other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and lower reimbursement, and in additional downward pressure on the price that we receive for any approved product.

PRC Regulation

We are subject to a variety of PRC laws, rules and regulations affecting many aspects of our business. This section sets out a summary of the major relevant laws, regulations, rules and policies which may have material impact on our business and operations.

Regulations on Company Establishment and Foreign Investment

The establishment, operation and management of corporate entities in China are governed by the Company Law of PRC, or the PRC Company Law, which was promulgated by the Standing Committee of the National People's Congress, or the Standing Committee of the NPC, in December 1993 and further amended in December 1999, August 2004, October 2005, December 2013 and October 2018, respectively. According to the PRC Company Law, companies are generally classified into two categories: limited liability companies and companies limited by shares. The PRC Company Law also applies to foreign-invested limited liability companies. According to the PRC Company Law, where laws on foreign investment have other stipulations, such stipulations shall prevail.

Investment activities in the PRC by foreign investors are governed by the Catalog of Encouraged Industries for Foreign Investment (2022 Edition), which was promulgated by the National Development and Reform Commission, or the NDRC, and Ministry of Commerce of the PRC, or the MOFCOM, in October 2022 and came into effect in January 2023, and the Special Administrative Measures for the Access of Foreign Investment (Negative List), or the Negative List, which was promulgated by the MOFCOM and the NDRC in December 2021 and came into effect in January 2022. The Negative List sets out the restrictive measures in a unified manner, such as the requirements on shareholding percentages and management, for the access of foreign investments, and the industries that are prohibited from receiving foreign investment. The Negative List covers 12 industries, and any field not falling under the Negative List shall be administered under the principle of equal treatment to domestic and foreign investment.

Foreign Investment Law of the PRC, or the Foreign Investment Law, was promulgated by the National People's Congress, or the NPC in March 2019 and came into effect in January 2020. When the Foreign Investment Law came into effect, the Law on Wholly Foreign-owned Enterprises of the PRC, the Law on Sino-foreign Equity Joint Ventures of the PRC and the Law on Sino-foreign Cooperative Joint Ventures of the PRC were repealed simultaneously. The investment activities of foreign natural persons, enterprises or other organizations (collectively, the "foreign investors") directly or indirectly within the territory of China shall comply with and be governed by the Foreign Investment Law. Such activities include: 1) establishing by foreign investors of foreign-invested enterprises in China alone or jointly with other investors; 2) acquiring by foreign investors of shares, equity, property shares, or other similar interests of Chinese domestic enterprises; 3) investing by foreign investors in new projects in China alone or jointly with other investors; and 4) other forms of investment prescribed by laws, administrative regulations or the State Council.

In December 2019, the State Council promulgated the Regulations on Implementing the Foreign Investment Law of the PRC, which came into effect in January 2020. When the Regulations on Implementing the Foreign Investment Law of the PRC came into effect, the Regulation on Implementing the Sino-Foreign Equity Joint Venture Enterprise Law of the PRC, Provisional Regulations on the Duration of Sino-Foreign Equity Joint Venture Enterprise, the Regulations on Implementing the Wholly Foreign-Invested Enterprise Law of the PRC and the Regulations on Implementing the Sino-Foreign Cooperative Joint Venture Enterprise Law of the PRC were repealed simultaneously.

In December 2019, the MOFCOM and the State Administration for Market Regulation, or the SAMR promulgated the Measures on Reporting of Foreign Investment Information, which came into effect in January 2020. When the Measures on Reporting of Foreign Investment Information came into effect, the Interim Measures for the Administration of Filing for Establishment and Changes in Foreign Investment Enterprises were repealed simultaneously. Since January 1, 2020, for foreign investors carrying out investment activities directly or indirectly in China, the foreign investors or foreign-invested enterprises shall submit investment information to the relevant commerce administrative authorities according to the Measure on Reporting of Foreign Investment Information.

Regulation on Pharmaceutical Product Development, Approval and Registration

Drug Regulatory Regime

The Drug Administration Law of the PRC, or the Drug Administration Law, was promulgated by the Standing Committee of the NPC, in September 1984. The two latest amendments to the Drug Administration Law were the amendment promulgated in April 2015 and in August 2019. The Regulations for the Implementation of the Drug Administration Law was promulgated by the State Council in August 2002, and was last amended in March 2019. The Drug Administration Law and the Regulations for the Implementation of the Drug Administration Law have jointly established the legal framework for the administration of pharmaceutical products in China, including the research, development and manufacturing of new drugs. The Drug Administration Law applies to entities and individuals engaged in the development, production, trade, application, supervision and administration of pharmaceutical products. It regulates and provides for a framework for the administration of pharmaceutical manufacturers, pharmaceutical trading companies and medicinal preparations of medical institutions, and the development, research, manufacturing, distribution, packaging, pricing and advertisements of pharmaceutical products. The Regulations for the Implementation of the Drug Administration Law, at the same time, provide the detailed implementation regulations for the Drug Administration Law.

In 2017, the drug regulatory system entered a new and significant period of reform. The General Office of the State Council and the General Committee of China Communist Party jointly issued Opinions on Deepening the Reform of the Evaluation and Approval Systems and Encouraging Innovation on Drugs and Medical Devices, or the Innovation Opinions. The expedited programs, the record-filing system, the prioritized review mechanism, the acceptance of foreign clinical data under the Innovation Opinions and other recent reforms encourage drug manufacturers to seek marketing approval in China first for the development of drugs in highly prioritized therapeutic areas, such as oncology or rare diseases.

To implement the regulatory reform introduced by Innovation Opinions, the Standing Committee of the NPC, the National Medical Products Administration, or the NMPA, a newly formed government authority as well as other authorities, are currently responsible for revising the laws, regulations and rules governing the pharmaceutical products and the industry.

In August 2019, the Standing Committee of the NPC promulgated the new Drug Administration Law, or the 2019 Amendment, which came into effect in December 2019. The 2019 Amendment contains many of the major reform initiatives implemented by the Chinese government since 2015, including but not limited to the Marketing Authorization Holder, or the MAH, system, conditional approvals of drugs, traceability system of drugs, and the cancellation of relevant certification according to the Good Manufacturing Practice, or the GMP, and the Good Supply Practice, or the GSP.

Regulatory Authorities

Pharmaceutical products in China are monitored and supervised on a national scale by the NMPA. The local provincial medical products administrative authorities are responsible for supervision and administration of drugs within their respective administrative regions. The NMPA was newly formed under the SAMR. The NMPA's predecessor, the State Drug Administration, or the SDA, was replaced by the State Food and Drug Administration, or the SFDA, which was later reorganized into the China Food and Drug Administration, or the CFDA, as part of the institutional reforms implemented by the State Council.

The primary responsibilities of the NMPA include:

- monitoring and supervising the administration of pharmaceutical products, medical appliances and equipment as well as cosmetics in the PRC;
- formulating administrative rules and policies concerning the supervision and administration of pharmaceutical, medical devices, and cosmetics industry;
- evaluating, registering and approving new drugs, generic drugs, imported drugs and traditional Chinese medicine;
- approving and issuing permits for the manufacture and export/import of pharmaceutical products, medical appliances and equipment;

- approving the establishment of enterprises to be engaged in the manufacture and distribution of pharmaceutical products;
- examining and evaluating the safety of pharmaceutical products, medical devices, and cosmetics; and
- managing significant accidents involving pharmaceutical products, medical devices and cosmetics.

In 2013, the Ministry of Health, or the MOH, and the National Population and Family Planning Commission were integrated into the National Health and Family Planning Commission of the PRC, or the NHFPC. In March 2018, the First Session of the Thirteenth NPC approved the State Council Institutional Reform Proposal, according to which, NHFPC and certain other governmental authorities were consolidated into the National Health Commission, or the NHC. The responsibilities of the NHC include coordinating the formulation of national drug policies, the national essential medicine system and the National Essential Medicines List and drafting the administrative rules for the procurement, distribution and use of national essential medicines.

According to the Decision of the CFDA on Adjusting the Approval Procedures under the Administrative Approval Items for Certain Drugs, which was promulgated by the CFDA in March 2017 and came into effect in May 2017, the Investigational New Drug Application, or the IND, approval should be issued by the Center for Drug Evaluation, or the CDE, on behalf of the CFDA.

Regulations on Clinical Trials and Registration of Drugs

Administrative Measures for Drug Registration

In July 2007, the SFDA promulgated the amended version of the Administrative Measures for Drug Registration, or the Registration Measures, which became effective in October 2007. The Registration Measures mainly cover: (1) definitions of drug registration applications and regulatory responsibilities of drug administration; (2) general requirements for drug registration, including application for registration of new drugs, generic drugs, imported drugs and supplemental application, as well as application for re-registration; (3) clinical trials; (4) application, examination and approval of new drugs, generic drugs and imported drugs; (5) supplemental applications and re-registrations of drugs; (6) inspections; (7) registration standards and specifications; (8) time limit; (9) re-examination; and (10) liabilities and other supplementary provisions.

According to the Registration Measures, drug registration applications are divided into three different types, namely Domestic New Drug Application, Domestic Generic Drug Application and Imported Drug Application. Drugs which fall into one of three general types are divided according to the drug's working mechanism, namely whether the drug is classified as a chemical medicine, a biological product, a traditional Chinese medicine or a natural medicine. New Drug Application, or NDA, refers to an application for registration of a drug that has not yet been marketed for sale in China. In addition, the registration of drugs that change the dosage form of the marketed drugs, change the route of administration and increase the new indications shall be reported in accordance with the application procedures for new drugs. Under the Registration Measures, a Category 1 drug refers to a new drug that has never been marketed in any country, and such drug is eligible for special review or fast track approval by the NMPA.

In January 2020, the SAMR released the amended Administrative Measures for Drug Registration, or the Amended Registration Measures, which came into effect in July 2020. The Amended Registration Measures provide detailed procedural and substantive requirements for the key regulatory concepts established by the Drug Administration Law, and confirms a number of reform actions that have been taken in the past years, including but not limited to: (i) the full implementation of the MAH system and implied approval of the commencement of clinical trial; (ii) the implementation of associated review of drugs, excipients and packaging materials; and (iii) the introduction of four procedures for expedited registration of drugs, which are procedures for ground-breaking therapeutic drugs, procedures for conditional approval, procedures for prioritized reviews and approval, and procedures for special examination and approval. Detailed implementation rules for drug classification and requirements for corresponding application materials will be promulgated by the NMPA.

In March 2016, the CFDA issued the Reform Plan for Registration Category of Chemical Medicine, which outlined the reclassifications of drug applications under the Registration Measures. According to the Reform Plan for Registration Category of Chemical Medicine, Category 1 drugs refer to innovative new drugs that have not been marketed anywhere in the world. Improved new drugs that are not marketed anywhere in the world fall into Category 2 drugs. Generic drugs, that have equivalent quality and efficacy to the originator's drugs and have been marketed abroad but not yet in China, can be classified as Category 3 drugs. Generic drugs, that have equivalent quality and efficacy to the originator's drugs and have been marketed in China, fall into Category 4 drugs. Category 5 drugs are drugs which have already been marketed abroad, but are not yet approved in China. Category 1 drugs and Category 5 drugs can be registered through the Domestic New Drug Application and the Imported Drug Application Procedures under the Registration Measures, respectively.

The SFDA promulgated the Administrative Provisions on Special Examination and Approval of Registration of New Drugs in January 2009, according to which, the SFDA conducts special examination and approval for new drug registration applications when: (1) the effective constituent of drug extracted from plants, animals, minerals, etc., as well as the preparations thereof have never been marketed in China, and the material medicines and the preparations thereof are newly discovered; (2) the chemical raw material medicines as well as the preparations thereof and the biological product have not been approved for marketing at home and abroad; (3) the new drugs have obvious clinical treatment advantages for such diseases as AIDS, malignant tumors and orphan diseases, etc. or (4) the new drugs treat diseases currently with no effective methods of treatment.

The Special Examination and Approval of Registration of New Drugs provides that the applicant may file for special examination and approval at the clinical trial application stage if the product candidate falls within items (1) or (2). The provisions provide that for product candidates that fall within items (3) or (4), the application for special examination and approval cannot be made until filing for production.

Accelerated Approval for Clinical Trial and Registration

The Innovation Opinions established a framework for reforming the evaluation and approval system for drugs, medical devices and equipment. The Innovation Opinions enhanced the standard of approval for drug registration and accelerated the evaluation and approval process for innovative drugs as well as drug clinical trials.

The CFDA released the Circular Concerning Several Policies on Drug Registration Review and Approval in November 2015, which further clarified the measures and policies for simplifying and accelerating the approval process of clinical trials, including:

- a one-time umbrella approval procedure allowing the overall approval of all phases of a new drug's clinical trials, replacing the current phase-by-phase application and approval procedure; and

- a fast track drug registration or clinical trial approval pathway for the following applications: (1) registration of innovative new drugs for treating HIV, cancer, serious infectious diseases and orphan diseases, etc.; (2) registration of pediatric drugs; (3) registration of geriatric drugs and drugs treating PRC-prevalent diseases in elders; (4) registration of drugs listed in national major science and technology projects or national key research and development plan; (5) registration of clinical urgently needed drugs using advanced technology, using innovative treatment methods, or having distinctive clinical benefits; (6) registration of foreign innovative drugs to be manufactured locally in China; (7) concurrent applications for new drug clinical trials which are already approved in the United States or EU or concurrent drug registration applications for drugs which have applied to the competent drug approval authorities for marketing authorization and passed such authorities' onsite inspections in the United States or EU and are manufactured using the same production line in China; and (8) clinical trial applications for drugs with urgent clinical need and patent expiry within three years, and manufacturing authorization applications for drugs with urgent clinical need and patent expiry within one year.

The NMPA released the Circular on Adjusting Evaluation and Approval procedures for Clinical Trials for Drugs in July 2018, according to which, within 60 days after the acceptance of and the fees paid for the IND application, the applicant may conduct the clinical trials for the drug in accordance with the clinical trial protocol submitted, if the applicant has not received any negative or questioning opinion from the CDE. Such approval process has been further enacted into the 2019 Amendment.

Trial Exemptions and Acceptance of Foreign Data

The NMPA issued the Technical Guidance Principles on Accepting Foreign Drug Clinical Trial Data in July 2018, as one of the implementing rules for the Innovation Opinions, which provides that overseas clinical data can be submitted for the drug registration applications in China. Such applications can be in the form of waivers to China-based clinical trials, bridging trials and direct NDAs. According to the Technical Guidance Principles on Accepting Foreign Drug Clinical Trial Data, sponsors may use the data of foreign clinical trials to support drug registration in China, provided that sponsors must ensure the authenticity, completeness, accuracy and traceability of foreign clinical trial data and such data must be obtained consistent with the relevant requirements under the Good Clinical Trial Practice of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, or the ICH. Sponsors must also comply with other relevant sections of the Registration Measures when applying for drug registrations in China using foreign clinical trial data.

The NMPA now officially permits, and its predecessor agencies have permitted on a case-by-case basis in the past, drugs approved outside of China to be approved in China on a conditional basis without pre-approval clinical trials being conducted in China. Specifically, the NMPA and the NHC released the Procedures for Reviewing and Approval of Clinical Urgently Needed Overseas New Drugs in October 2018, permitting drugs that have been approved within the last ten years in the United States, the EU or Japan and that prevent or treat orphan diseases, or prevent or treat serious life-threatening illnesses for which there is either no effective therapy in China, or for which the foreign-approved drug would have clear clinical advantages. Applicants will be required to establish a risk mitigation plan and may be required to complete trials in China after the drug has been marketed. The CDE has developed a list of qualifying drugs that meet the foregoing criteria.

Clinical Trial Process and Good Clinical Practices

According to the Registration Measures, a clinical trial consists of Phases I, II, III and IV. Phase I refers to the initial clinical pharmacology and safety evaluation studies in humans. Phase II refers to the preliminary evaluation of a product candidate’s therapeutic effectiveness and safety for particular indications in patients, to provide evidence and support for the design of Phase III clinical trials and to settle the administrative dose regimen. Phase III refers clinical trials undertaken to confirm the therapeutic effectiveness and safety on patients with target indications, to evaluate the overall benefit-risk relationships of the drug, and ultimately to provide sufficient evidence for the review of drug registration application. Phase IV refers to a new drug’s post-marketing study to assess therapeutic effectiveness and adverse reactions when the drug is widely used, to evaluate the overall benefit-risk relationships of the drug when used among the general population or specific groups and to adjust the administration dose.

To improve the quality of clinical trials, the SFDA promulgated the Good Clinical Trial Practice for Drugs in August 2003, or the GCP Rules, which was replaced by the revised Good Clinical Trial Practice for Drugs, the Revised GCP Rules, promulgated by the NMPA and the NHC in April 2020 and coming into effect in July 2020. According to the Administration of Quality of Drug Clinical Practice, clinical trial means systematical investigation of drugs conducted on human subjects (patients or healthy volunteers) to prove or reveal the function, adverse reactions and/or absorption, distribution, metabolism and excretion of the drug being investigated. The purpose of a clinical trial is to determine the therapeutic efficacy and safety of the drug. The Revised GCP Rules provide comprehensive and substantive requirements on the design and conduct of clinical trials in China. In particular, the Revised GCP Rules enhance the protection for study subjects and tighten the control over bio-samples collected under clinical trials.

The Revised GCP Rules also set out the qualifications and requirements for the investigators and centers participating in clinical trial, who must: (i) have professional certification at a clinical trial center, professional knowledge, training experience and capability of clinical trial, and be able to provide the latest resume and relevant qualification documents per request; (ii) be familiar with the trial protocol, investigator’s brochure and relevant information of the trial drug provided by the applicant; (iii) be familiar with and comply with the Revised GCP Rules and relevant laws and regulations relating to clinical trials; (iv) keep a copy of the authorization form on work allocation signed by investigators; (v) accept supervision and inspection organized by the applicant and inspection by the drug regulatory authorities; and (vi) in the case of investigators and clinical trial centers authorizing other individual or institution to undertake certain responsibilities and functions relating to clinical trial, they shall ensure such individual or institution are qualified and establish complete procedures to ensure the responsibilities and functions are fully performed and generate reliable data.

Communication with the CDE

According to the Circular on Adjusting Evaluation and Approval Procedures for Clinical Trials for Drugs, where the application for clinical trial of new investigational drug has been approved, upon the completion of Phases I and II clinical trials and prior to Phase III clinical trial, the applicant shall submit the application for Communication Session to the CDE to discuss the key technical questions including the design of Phase III clinical trial protocol. Within 60 days after the acceptance of and the fees paid for the IND application, the applicant may conduct the clinical trials for the drug in accordance with the clinical trial protocol submitted, if the applicant has not received any negative or questioning opinion from the CDE.

The NMPA promulgated the Administrative Measures for Communication on the Research, Development and Technical Evaluation of Drugs in December 2020, according to which, during the research and development periods and in the registration applications of traditional Chinese medicines, chemical drugs and biological products, the applicants may propose to conduct communication meetings with the CDE on key technologies and other issues not covered in the existing guidelines for drug research, development and evaluation during the process of technical evaluation of drug research, development and registration. The communication meetings can be classified into three types. Type I meetings are convened to address key safety issues in clinical trials of drugs and key technical issues in the research and development of breakthrough therapeutic drugs. Type II meetings are held during the key research and development periods of drugs, mainly including meetings before the IND application, meetings upon the completion of Phase II trials and before the commencement of Phase III trials, meetings before submitting a marketing application for a new drug, and meetings for risk evaluation and control. Type III meetings refer to meetings not classified as Type I or Type II.

Drug Clinical Trial Registration

According to the Registration Measures, upon obtaining the approval of its IND applications and before conducting a clinical trial, an applicant shall file a registration form with the SFDA containing various details, including the clinical trial protocol, the name of the principal researcher of the leading institution, the names of participating institutions and researchers, an approval letter from the ethics committee, and a sample of the informed consent form, with a copy sent to the competent provincial administration departments where the trial institutions will be located. The CFDA released the Announcement on Drug Clinical Trial Information Platform in September 2013, according to which, instead of the aforementioned registration field with the CFDA, all clinical trials approved by the CFDA and conducted in China shall complete a clinical trial registration and publish trial information through the Drug Clinical Trial Information Platform. The applicant shall complete the trial pre-registration within one month after obtaining the approval of the clinical trial approval in order to obtain the trial's unique registration number and complete registration of certain follow-up information before the first subject's enrollment in the trial. If the registration is not completed within one year after the approval of the IND applications, the applicant shall submit an explanation, and if the first submission is not completed within three years, the approval of the IND applications shall automatically expire.

New Drug Application

According to the Registration Measures, drug registration applications include domestic NDA, domestic generic drug application and imported drug application. Drugs are classified into chemical drugs, biological products and traditional Chinese medicine or natural drugs. When Phases I, II and III clinical trials have been completed, the applicant may apply to the SFDA for approval of the NDA. The SFDA then determines whether to approve the application according to the comprehensive evaluation opinion provided by the CDE.

Pilot Plan for the MAH System

The Innovation Opinions provide a pilot plan for the MAH system.

Under the authorization of the Standing Committee of the NPC, the General Office of the State Council issued the Pilot Plan for the Drug Marketing Authorization Holder Mechanism in May 2016, which provides a detailed pilot plan for the MAH system in 10 Chinese provinces. Under the MAH system, domestic drug research and development institutions and individuals in the pilot regions are eligible to be holders of drug registrations without having to become drug manufacturers. The marketing authorization holders may engage contract manufacturers for manufacturing, provided that the contract manufacturers are licensed and located within the pilot regions. Drugs that qualify for the MAH system are: (1) new drugs (including but not limited to drugs under category I to category IV of chemical drugs, and targeted preparation, sustained release preparation, controlled release preparation under category V of chemical drugs, biological products approved as category I and VII drugs and biosimilars under the Registration Measures) approved after the implementation of the MAH system; (2) generic drugs approved as category III or IV drugs under the Reform Plan for Registration Category of Chemical Medicine; (3) previously approved generics that have passed equivalence assessments against original drugs; and (4) previously approved drugs whose licenses were held by drug manufacturers originally located within the pilot regions, but which have moved out of the pilot regions due to corporate mergers or other reasons.

The CFDA promulgated the Circular on the Matters Relating to Promotion of the Pilot Program for the Drug Marketing Authorization Holder System in August 2017. It clarified the legal liability of the MAH, who is responsible for managing the whole manufacturing and marketing chain and the whole life cycle of drugs and legally liable for preclinical drug study, clinical trials, manufacturing, marketing, distribution and adverse drug reaction monitoring. According to the Circular on the Matters Relating to Promotion of the Pilot Program for the Drug Marketing Authorization Holder System, the MAH shall submit a report of drug manufacturing, marketing, prescription, techniques, pharmacovigilance, quality control measures and other situations to the CFDA within 20 working days after the end of each year.

According to the Pilot Plan for the Drug Marketing Authorization Holder Mechanism, the pilot plan was originally set for a three-year period and was scheduled to expire in November 2018. The Standing Committee of the NPC promulgated the Decision of Extending the Pilot Period of Authorizing the State Council to Carry Out the Pilot Plan for the Drug Marketing Authorization Holder Mechanism in Certain Places in October 2018, which extended the term of the MAH system to November 4, 2019.

According to the 2019 Amendment, which came into effect on December 1, 2019, the MAH system will be applicable throughout the country and the legal representative and the key person-in-charge of a drug MAH shall be fully responsible for the quality of drugs.

International Multi-Center Clinical Trials

The International Multi-Center Clinical Trial Guidelines (Trial), or the Multi-Center Clinical Trial Guidelines, which was promulgated by the CFDA in January 2015 and came into effect in March 2015, provided guidance on the implementation of Multi-Regional Clinical Trials, or the MRCT, in China. According to the Multi-Center Clinical Trial Guidelines, international multi-center clinical trial applicants may simultaneously perform clinical trials in different centers using the same clinical trial protocol. Where the applicants plan to implement the international multi-center clinical trials in the PRC, the applicants shall comply with relevant laws and regulations, such as the Drug Administration Law, the Implementing Regulations of the Drug Administration Law and the Registration Measures, execute the GCP Rules, make reference to universal international principles such as the ICH-GCP and comply with the laws and regulations of the countries involved in the international multi-center clinical trials. Where the applicants plan to use the data derived from the international multi-center clinical trials for approval of a drug registration in the PRC, it shall involve at least two countries, including China, and shall satisfy the requirements for clinical trials set forth in the Multi-Center Clinical Trial Guidelines, Registration Measures and other related laws and regulations.

In April 2020, the NMPA and the NHC promulgated the Revised GCP Rules, which came into effect in July 2020. The Revised GCP Rules summarize the requirements for initiating an MRCT, that is, before initiating an MRCT: (i) the applicant shall ensure that all the centers participating in the clinical trial comply with the trial protocol; (ii) the applicant shall provide each center with the same trial protocol, and each center shall comply with the same unified evaluation criterion for clinical trial and laboratory data and the same guidance for case report form; (iii) each center shall use the same case report form to record the data of each human subject obtained during the trial; (iv) before initiating a clinical trial, a written document is required to specify the responsibilities of the investigators of each center; and (v) the applicant shall ensure the communication among the investigators of each center.

Data derived from international multi-center clinical trials can be used for the new drug applications with the NMPA. When using international multi-center clinical trial data to support new drug applications in China, applicants shall submit the completed global clinical trial report, statistical analysis report and database, along with relevant supporting data in accordance with the content and format requirements under the International Conference on Harmonization-Common Technical Document; subgroup research results summary and comparative analysis shall also be conducted concurrently. Leveraging the clinical trial data derived from international multi-center clinical trials conducted by our partners, we may avoid unnecessarily repetitive clinical trials and thus further accelerate the NDA process in China.

The CFDA released the Decision on Adjusting Items concerning the Administration of Imported Drug Registration in October 2017, which includes the following key points:

- If the International Multicenter Clinical Trial, or the IMCCT, of a drug is conducted in China, Phase I clinical trial of the drug is allowed simultaneously. The IMCCT drug does not need to be approved or to enter into either a Phase II or III clinical trial in a foreign country, except for preventive biological products;
- If the IMCCT is conducted in China, the application for drug marketing authorization can be submitted directly after the completion of the IMCCT. The Registration Measures and relevant laws and regulations shall be complied with for registration application;
- With respect to applications for clinical trial and marketing of the imported innovative chemical drugs and therapeutic biological products, the marketing authorization in the country or region where the foreign drug manufacturer is located will not be required; and
- With respect to drug applications that have been accepted before the release of this Decision, if relevant requirements are met, importation permission can be granted if such applications request exemption of clinical trials for the imported drugs based on the data generated from the IMCCT.

Approval of Human Genetic Resources

The Interim Administrative Measures on Human Genetic Resources, promulgated by the Ministry of Science and Technology and the MOH in June 1998, aimed at protecting and fairly utilizing human genetic resources in the PRC. The Ministry of Science and Technology promulgated the Service Guide for Administrative Licensing Items concerning Examination and Approval of Sampling, Collecting, Trading or Exporting Human Genetic Resources, or Taking Such Resources out of the PRC in July 2015, according to which, the sampling, collection or research activities of human genetic resources by a foreign-invested sponsor fall within the scope of international cooperation, and the cooperating Chinese organization shall apply for approval of the China Human Genetic Resources Management Office through an online system. The Ministry of Science and Technology further promulgated the Circular on Optimizing the Administrative Examination and Approval of Human Genetic Resources in October 2017 and October 2020, which became effective in December 2017 and October 2020, respectively and simplified the approval of sampling and collecting human genetic resources for listing a drug in the PRC.

The Regulations of the PRC on the Administration of Human Genetic Resources, which was promulgated by the State Council in May 2019 and came into effect in July 2019, further stipulates that, in order to obtain marketing authorization for relevant drugs and medical devices in China, no approval is required in international clinical trial cooperation using China's human genetic resources at clinical institutions without export of human genetic resource materials. However, the type, quantity and usage of the human genetic resource to be used shall be filed with the administrative department of science and technology under the State Council before clinical trials.

The Bio-security Law of the PRC promulgated by the Standing Committee of the NPC in October 2020, and took effect in April 2021, provides that the state shall have sovereignty over the human genetic resources and biological resources of the PRC. The Bio-security Law of the PRC further stipulates that the department of science and technology under the State Council shall be the competent authority for the approval or filing of using China's human genetic resources.

Regulations on Drug Manufacturing and Distribution

Drug Manufacturing

According to the Drug Administration Law and the Implementing Regulations of the Drug Administration Law, a drug manufacturing enterprise is required to obtain a drug manufacturing license from the relevant provincial drug administration authority of the PRC. The grant of such license is subject to an inspection of the manufacturing facilities, and an inspection to determine whether the sanitary condition, quality assurance systems, management structure and equipment meet the required standards. According to the Implementing Regulations of the Drug Administration Law and the Measures on the Supervision and Administration of the Manufacture of Drugs, which was promulgated in August 2004, amended in November 2017 and January 2020 and came into effect in July 2020, the drug manufacturing license is valid for five years and shall be renewed at least six months prior to its expiration date upon a re-examination by the relevant authority. In addition, the name, legal representative, registered address and type of the enterprise specified in the drug manufacturing certificate shall be identical to that set forth in the business license as approved and issued by the industrial and commercial administrative department. To the extent the MAH does not manufacture the drug internally but through a contract manufacturing organization, the MAH shall apply for drug manufacturing license with the provincial counterpart of the NMPA, subject itself to inspections and other regulatory oversight by the agency.

The Good Manufacturing Practice for Drugs was promulgated in March 1988 and was amended in December 1992 and June 1999 and January 2011. The latest amendment was in June 2020 and came into effect in October 2020. The Good Manufacturing Practice for Drugs comprises a set of detailed standard guidelines governing the manufacture of drugs, which include institution and staff qualifications, production premises and facilities, equipment, hygiene conditions, production management, quality controls, product operation, raw material management, maintenance of sales records, management of customer complaints and adverse event reports.

Drug Distribution

According to the Drug Administration Law, its implementing regulations and the Measures for the Supervision and Administration of Circulation of Pharmaceuticals, which was approved by the SFDA in December 2006 and came into effect in May 2007, pharmaceutical enterprises shall be responsible for the quality of the pharmaceuticals that they manufacture, operate, use, purchase, sell, transport, or store.

According to the Measures for the Administration of Pharmaceutical Operation Certificate, which was promulgated in February 2004 and amended in November 2017 by the CFDA, a Medicine Operation Certificate is valid for five years. Each holder of the Medicine Operation Certificate must apply for an extension of its permit six months prior to expiration. The establishment of a wholesale pharmaceutical distribution company requires the approval of provincial medicine administrative authorities. Upon approval, the authority will grant a Medicine Operation Certificate in respect of the wholesale pharmaceutical product distribution company. The establishment of a retail pharmacy store requires the approval of the local medicine administrative authorities at or above the county level. Upon approval, the authority will grant a Medicine Operation Certificate in respect of the retail pharmacy store.

Other PRC Government Regulations

Regulations on Intellectual Property Rights

In terms of international conventions, China has entered into (including but not limited to) the Agreement on Trade-Related Aspects of Intellectual Property Rights, the Paris Convention for the Protection of Industrial Property, the Madrid Agreement Concerning the International Registration of Marks and the Patent Cooperation Treaty.

Patents

According to the Patent Law of the PRC, which was promulgated by the Standing Committee of the NPC in March 1984, amended in September 1992, August 2000, December 2008 and October 2020, and came into effect in June 2021, and the Implementation Rules of the Patent Law of the PRC, which was promulgated by the State Council in June 2001 and amended in December 2002 and January 2010, there are three types of patents in the PRC: invention patents, utility model patents and design patents. The protection period is 20 years for an invention patent and 10 years for a utility model patent and 15 years for a design patent, commencing from their respective application dates. For the purpose of compensating for the time taken to evaluate and approve a new drug to be put on market, the patent administrative department under the State Council shall grant compensation for duration of patent rights for invention of a new drug approved to be put on market in the PRC upon request of the patentee. The compensation period shall not exceed five years, and the total validity period of patent rights for a new drug approved to be put on market shall not exceed 14 years.

In the process of evaluation and approval of marketing of a drug, where a dispute arises over the patent rights relating to the drug for which registration is applied between a drug marketing authorization applicant and a relevant patentee or interested party, the relevant party may file a lawsuit with a people's court, requesting a ruling on whether the relevant technical solution of the drug for which registration is applied falls within the scope of protection of others' drug patent rights. The drug regulatory department under the State Council may, within the stipulated period, make a decision on whether to suspend the approval of marketing of the drug concerned based on the effective judgment made by the people's court. A drug marketing authorization applicant and a relevant patentee or interested party may also request an administrative ruling from the patent administrative department under the State Council in respect of a dispute over patent rights relating to the drug for which registration is applied.

Any individual or entity that utilizes a patent or conducts any other activities that infringe a patent without prior authorization of the patent holder shall pay compensation to the patent holder and is subject to a fine imposed by relevant administrative authorities and, if constituting a crime, shall be held criminally liable in accordance with the law. According to the Patent Law of the PRC, any organization or individual that applies for a patent in a foreign country for an invention or utility model patent established in China is required to report to the NIPA for confidentiality examination.

Trade Secrets

According to the PRC Anti-Unfair Competition Law, which was promulgated by the Standing Committee of the NPC in September 1993 and amended in November 2017 and April 2019, respectively, the term “trade secrets” refers to technical and business information that is unknown to the public, has utility, may create business interests or profits for its legal owners or holders, and is maintained as a secret by its legal owners or holders. Under the PRC Anti-Unfair Competition Law, business persons are prohibited from infringing others’ trade secrets by: (1) obtaining the trade secrets from the legal owners or holders by any unfair methods such as theft, bribery, fraud, coercion, electronic intrusion, or any other illicit means; (2) disclosing, using or permitting others to use the trade secrets obtained illegally under item (1) above; (3) disclosing, using or permitting others to use the trade secrets, in violation of any contractual agreements or any requirements of the legal owners or holders to keep such trade secrets in confidence; or (4) instigating, inducing or assisting others to violate a confidentiality obligation or to violate a rights holder’s requirements on keeping confidentiality of trade secrets, disclosing, using or permitting others to use the trade secrets of the rights holder. If a third party knows or should have known of the above-mentioned illegal conduct but nevertheless obtains, uses or discloses trade secrets of others, the third party may be deemed to have committed a misappropriation of the others’ trade secrets. The parties whose trade secrets are being misappropriated may petition for administrative corrections, and regulatory authorities may stop any illegal activities and fine infringing parties.

Trademarks

According to the Trademark Law of the PRC promulgated by the Standing Committee of the NPC in August 1982, and amended in February 1993, October 2001, August 2013 and April 2019, respectively, the period of validity for a registered trademark is ten years, commencing on the date of registration. The registrant shall go through the formalities for renewal within twelve months prior to the expiry date of the trademark if continued use is intended. Where the registrant fails to do so, a grace period of six months may be granted. The validity period for each renewal of registration is ten years, commencing on the day immediately after the expiry of the preceding period of validity for the trademark. In the absence of a renewal upon expiry, the registered trademark shall be cancelled. Industrial and commercial administrative authorities have the authority to investigate any behavior that infringes the exclusive right under a registered trademark in accordance with the law. In case of a suspected criminal offense, the case shall be timely referred to a judicial authority and decided according to the law.

Domain Names

Domain names are protected under the Administrative Measures on the Internet Domain Names, which was promulgated by the Ministry of Industry and Information Technology in August 2017, and the Implementing Rules on Registration of National Top-level Domain Names, which was promulgated by China Internet Network Information Center in and came into effect in June 2019. The Ministry of Industry and Information Technology is the main regulatory body responsible for the administration of PRC internet domain names. Domain name registrations are handled through domain name service agencies established under the relevant regulations, and the applicants become domain name holders upon successful registration.

Regulations on Information Security and Data Protection

Scientific data

In March 2018, the General Office of the State Council of the PRC promulgated the Measures for the Management of Scientific Data, or the Scientific Data Measures, which provide a broad definition of scientific data and relevant rules for the management of scientific data. Pursuant to the Scientific Data Measures, the scientific data involving state secrets, national security, social or public interests, trade secrets and individual privacy shall be kept confidential; where it is necessary to disclose such data, the purposes of utilization, qualifications of users and confidentiality conditions, among others shall be examined, and the scope of those with access thereto shall be strictly controlled. Enterprises in the PRC must seek governmental approval before any scientific data involving a state secret is provided during foreign contacts and cooperation. Upon approval by the competent departments, corporate entities shall undergo the relevant formalities as required, and sign confidentiality agreements with users. Furthermore, any researcher conducting research funded in part or in whole by the PRC government is required to submit relevant scientific data for management by the entity to which such researcher is affiliated before that data may be published in any foreign academic journal.

Personal data

Pursuant to the Civil Code of the PRC, the personal information of an individual shall be protected by the law. Any organization or individual that needs to obtain personal information of others shall obtain such information legally and ensure the safety of such information, and shall not illegally collect, use, process or transmit personal information of others, or illegally purchase or sell, provide or publish personal information of others. In addition, the processing of personal information shall follow the principles of lawfulness, appropriateness and necessity.

In August 2021, the Personal Information Protection Law of the PRC promulgated by the Standing Committee of the NPC and took into effect in November 2021. The Personal Information Protection Law of the PRC shall apply to the processing of the personal information of natural persons within the territory of the PRC under any of the following circumstances: (i) where the purpose is to provide domestic natural persons with products or services; (ii) where the activities of domestic natural persons are analyzed and evaluated; and (iii) other circumstances as prescribed by laws and administrative regulations. The processing of personal information shall follow the principles of lawfulness, legitimacy, necessity and good faith, and it is not allowed to process personal information by misleading, fraud, coercion or otherwise.

Information security and review

On November 7, 2016, the Standing Committee of NPC promulgated the Cybersecurity Law of the PRC, which became effective on June 1, 2017, pursuant to which, network operators shall fulfill their obligations to safeguard security of the network when conducting business and providing services. Those who provide services through networks shall take technical measures and other necessary measures pursuant to laws, regulations and compulsory national requirements to safeguard the safe and stable operation of the networks, respond to network security incidents effectively, prevent illegal and criminal activities, and maintain the integrity, confidentiality and usability of network data. Network operator shall not collect the personal information irrelevant to the services it provides or collect or use the personal information in violation of the provisions of laws or agreements concluded with its users, and network operators of key information infrastructure shall store within the PRC all the personal information and important data collected and produced within the PRC. The purchase of network products and services that may affect national security shall be subject to national cybersecurity review.

On June 10, 2021, the Standing Committee of NPC promulgated the Data Security Law of the PRC, or the Data Security Law, which came into effect on September 1, 2021. The Data Security Law sets forth the regulatory framework and the responsibilities of the relevant governmental authorities in regulating data security. It provides that the central government shall establish a central data security work liaison system, which shall coordinate the relevant authorities covering different industries to formulate the catalogs of key data, and the special measures that shall be taken to protect the security of the key data. In addition, the Data Security Law provides that important data processors shall appoint a data security officer and a management department to take charge of data security, and such processors shall evaluate the risk of their data activities periodically and file assessment reports with the relevant regulatory authorities. Violation of Data Security Law may subject the relevant entities or individuals to warning, fines, business suspension, revocation of permits or business licenses, or even criminal liabilities.

On December 28, 2021, the Cybersecurity Review Measures was promulgated by Cyberspace Administration of China, State Development and Reform Commission, Ministry of Industry and Information Technology, Ministry of Public Security, Ministry of State Security, Ministry of Finance, Ministry of Commerce, People's Bank of China, SAMR, National Radio and Television Administration, CSRC, National Administration of State Secrets Protection and State Cryptography Administration and came into effect in February 2022. According to the Cybersecurity Review Measures, (i) the purchase of network products and services by a "critical information infrastructure operator" and the data processing activities of a "network platform operator" that affect or may affect national security shall be subject to the cybersecurity review; (ii) if a network platform operator who possesses personal information of more than 1 million users intends to go public in a foreign country, it must apply for a cybersecurity review with the Cybersecurity Review Office; and (iii) the relevant PRC governmental authorities may initiate cybersecurity review if they determine certain network products, services or data processing activities affect or may affect national security.

Furthermore, in July 2022, CAC issued the Measures on Security Assessment of the Cross-border Data Transfer, or the Security Assessment Measures, which provide that data processors shall make self-assessment of the risks before transferring data cross-border, and shall apply for security assessment for cross-border data transfer in any of the following circumstances: (i) outbound transfer of important data by a data processor; (ii) outbound transfer of personal information by CIIO Operators or a personal information processor who has processed the personal information of more than 1,000,000 people; (iii) outbound transfer of personal information by a personal information processor who has made outbound transfers of the personal information of 100,000 people cumulatively or the sensitive personal information of 10,000 people cumulatively since 1 January of the previous year; or (iv) other circumstances where an application for the security assessment of an outbound data transfer is required as prescribed by the national cyberspace administration authority.

On November 14, 2021, the CAC published the Regulations for the Administration of Cyber Data Security (Draft for Comment), or the Draft Data Security Regulations, for public comment by December 13, 2021. The Draft Data Security Regulations reiterate that a data processor who processes personal information of more than one million individuals must complete the cybersecurity review if it intends to be listed in a foreign country, and further stipulate that a data processor shall also apply for the cybersecurity review if it carries out data processing activities that affect or may affect national security. The Draft Data Security Regulations provide a broad definition of "data processing activities," including collection, storage, usage, processing, transfer, provision, publication, deletion and other activities, which covers the entire life cycle of data processing. The Draft Data Security Regulations also provide a broad definition of "data processor" as individuals and entities that may autonomously determine the purpose and method of data processing activities. In addition, the Draft Data Security Regulations require data processors which process important data or whose securities are listed outside of China to carry out data security assessment annually either by itself or through a third party data security service provider and submit the assessment report to a local agency of the CAC. The Draft Data Security Regulations remain silent on what constitutes a situation that "affects or may affect national security" and are subject to public comments and further changes before being formally adopted and entering into effect.

Regulations on Product Liability

In addition to the strict new drug approval process, certain PRC laws have been promulgated to protect the rights of consumers and to strengthen the control of medical products in the PRC. Under current PRC laws, manufacturers and vendors of defective products in the PRC may incur liability for loss and injury caused by such products. According to the General Principles of the Civil Law of the PRC promulgated in April 1986 and amended in August 2009 and General Rules of the Civil Law of the People's Republic of China promulgated in March 2017 and took effect in October 2017, the manufacturer or vendor of a defective product which causes property damage or physical injury to any person may be subject to civil liability for such damage or injury. In January 2021, the PRC Civil Code came into effect, the General Principles of the Civil Law of the PRC and General Rules of the Civil Law of the PRC were repealed simultaneously.

In February 1993, the Product Quality Law of the PRC, or the Product Quality Law, was promulgated aiming to protect the legitimate rights and interests of the end-users and consumers and to strengthen the supervision and control of the quality of products. The Product Quality Law was last revised in December 2018. According to the revised Product Quality Law, manufacturers who produce defective products may be subject to civil or criminal liability and have their business licenses revoked.

The Law of the PRC on the Protection of the Rights and Interests of Consumers was promulgated in October 1993 and amended in October 2013 to protect consumer rights when they purchase or use goods and services. According to which, all business operators must comply with this law when they manufacture or sell goods and/or provide services to customers. Under the latest amendment, all business operators shall protect the customers' privacy and keep any consumer information they obtain during the business operation strictly confidential. In addition, in extreme situations, pharmaceutical product manufacturers and operators may be subject to criminal liability if their goods or services lead to the death or injuries of customers or other third parties.

Regulations on Tort

According to the PRC Civil Code, if damages to other persons are caused by defective products due to the fault of third parties, such as the parties providing transportation or warehousing, the producers and the sellers of the products have the right to recover their respective losses from such third parties. If defective products are identified after they have been put into circulation, the producers or the sellers shall take remedial measures such as issuance of a warning, recall of products, etc., in a timely manner. The producers or the sellers shall be liable under tort if they fail to take remedial measures in a timely manner or have not made efforts to take remedial measures, thus causing damages. If the products are produced or sold with known defects, causing deaths or severe adverse health issues, the infringed party has the right to claim punitive damages in addition to compensatory damages.

Regulations on Environment Protection

Pursuant to the Environmental Protection Law of the PRC promulgated by the Standing Committee of the NPC, in December 1989, amended in April 2014 and effective in January 2015, any entity which discharges or will discharge pollutants during its course of operations or other activities must implement effective environmental protection safeguards and procedures to control and properly treat waste gas, waste water, waste residue, dust, malodorous gases, radioactive substances, noise vibrations, electromagnetic radiation and other hazards produced during such activities. According to the provisions of the Environmental Protection Law, in addition to other relevant laws and regulations of the PRC, the Ministry of Environmental Protection and its local counterparts take charge of administering and supervising said environmental protection matters.

Pursuant to the Environmental Protection Law, the environmental impact statement on any construction project must assess the pollution that the project is likely to produce and its impact on the environment, and stipulate preventive and curative measures; the statement shall be submitted to competent administrative department of environmental protection for approval. Installations for the prevention and control of pollution in construction projects must be designed, built and commissioned together with the principal part of the project.

Pursuant to the Law of the People's Republic of China on Environment Impact Assessment, which was promulgated in October 2002 and most recently amended in December 2018, the State implements a classification-based management on the environmental impact assessment of construction projects according to the impact of the construction projects on the environment. Construction units shall prepare an Environmental Impact Report or an Environmental Impact Statement, or fill out the Environmental Impact Registration Form.

Pursuant to the Regulations on Urban Drainage and Sewage Disposal, which was promulgated in October 2013 and came into effect in January 2014, and the Measures for the Administration of Permits for the Discharge of Urban Sewage into the Drainage Network, which was promulgated in December 2022 and came into effect in February 2023, drainage entities covered by urban drainage facilities shall discharge sewage into urban drainage facilities in accordance with the relevant provisions of the state. Where a drainage entity needs to discharge sewage into urban drainage facilities, it shall apply for a drainage license in accordance with the provisions of these Measures. The drainage entity that has not obtained the drainage license shall not discharge sewage into urban drainage facilities.

Regulations on Fire Protection

The Fire Prevention Law of the PRC, or the Fire Prevention Law, was adopted in April 1998 and last amended in April 2021. The Fire Prevention Law provides that fire control design and construction of a construction project shall comply with the State's fire control technical standards. Developers, designers, builders and project supervisors shall be responsible for the quality of the fire control design and construction of the construction project pursuant to the law. Development project fire safety design examinations and acceptance systems shall be implemented for development projects which are required to have fire safety design in accordance with the national fire protection technical standards.

According to the Eight Measures for the Public Security Fire Department to Deepen Reform and Serve Economic and Social Development promulgated by the Ministry of Public Security of the PRC in

August 2015, the fire protection design and completion acceptance fire protection record of construction projects with an investment of less than RMB300,000 or a building area of less than 300 square meters (or below the limit set by the housing and urban construction department of the provincial people's government) was no longer required.

Regulations on Overseas Securities Offering and Listing

In December 2021, the CSRC promulgated the Provisions of the State Council on the Administration of Overseas Securities Offering and Listing by Domestic Companies (Draft for Comments), or the Draft CSRC Administration Provisions, and the Administrative Measures for the Filing of Overseas Securities Offering and Listing by Domestic Companies (Draft for Comments), or the Draft CSRC Filing Measures, to regulate overseas offerings by domestic companies of equity shares, depository receipts, convertible corporate bonds, or other equity-like securities, and overseas listing of the securities for trading. Both direct and indirect overseas securities offering and listing by domestic companies would be regulated, of which the former refers to securities offering and listing in an overseas market made by a joint-stock company incorporated domestically, and the latter refers to securities offering and listing in an overseas market made in the name of an offshore entity.

Following issuance of the Draft CSRC Filing Measures, on February 17, 2023, the CSRC issued the Notice on Filing Arrangements for Overseas Securities Offering and Listing by Domestic Companies (the "CSRC Filing Notice"), stating that the CSRC has published the Trial Administrative Measures of Overseas Securities Offering and Listing by Domestic Companies (the "Trial Measures") and five supporting guidelines (the "Listing Guidelines"), collectively the Trial Measures and Listing Guidelines, which came into effect on March 31, 2023.

The Trial Measures provide that an overseas listing or offering securities (which, for the purposes of the Trial Measures, are defined thereunder as equity shares, depository receipts, corporate bonds convertible to equity shares, and other equity securities that are offered and listed overseas, either directly or indirectly, by PRC domestic companies) is explicitly prohibited under any of the following circumstances: (i) such securities offering and listing is explicitly prohibited by provisions in laws, administrative regulations and relevant state rules of the PRC; (ii) the intended securities offering and listing may endanger national security as reviewed and determined by competent authorities under the State Council in accordance with law; (iii) the domestic company, its controlling shareholder(s) or the actual controller have committed relevant crimes such as corruption, bribery, embezzlement, misappropriation of property or undermining the order of the socialist market economy during the latest three years; (iv) the domestic company is currently under investigations for suspicion of criminal offenses or major violations of laws and regulations, and no conclusion has yet been made thereof; or (v) there are material ownership disputes over equity held by the domestic company's controlling shareholder(s) or by other shareholder(s) that are controlled by the controlling shareholder(s) and/or actual controller.

A filing-based regulatory regime is adopted to regulate both direct and indirect overseas securities offering and listing by the domestic companies undert the Trial Measures. Direct overseas offering and listing by domestic companies refers to such overseas offering and listing by a joint-stock company incorporated domestically, while the indirect overseas offering and listing by domestic companies refers to the offering and listing by a company in the name of an overseas incorporated entity which major business operations are located domestically and such offering and listing is based on the underlying equity, assets, earnings or other similar rights of a domestic company.

The Trial Measures stipulate that an overseas listing will be determined as "indirect" if the issuer meets both of the following conditions: (1) 50% or more of any of the issuer's operating revenue, total profit, total assets or net assets as documented in its audited consolidated financial statements for the most recent accounting year are accounted for by PRC domestic companies ("Condition I"), and (2) the main parts of the issuer's business activities are conducted in the PRC, or its main places of business are located in the PRC, or the senior managers in charge of its business operations and management are mostly Chinese citizens or domiciled in the PRC ("Condition II"); whether Chinese citizens from Taiwan, Hong Kong, and Macau are included in the foregoing specification is not specified. The determination as to whether or not an overseas offering and listing by PRC domestic companies is indirect shall be made on a "substance over form" basis; the Listing Guidelines further stipulate that if an issuer not satisfying Condition I submits an application for issuance and listing in overseas markets in accordance with relevant non-PRC issuance regulations requiring such issuer to disclose risk factors mainly related to the PRC, the securities firm(s) and the issuer's PRC counsel should follow the principle of "substance over form" in order to identify and argue whether the issuer should complete a filing under the Trial Measures.

Subsequent securities offerings of an issuer in (i) the same overseas market where it has previously offered and listed securities, and (ii) an overseas market other than one where the issuer has previously offered and listed securities shall be filed with the CSRC within three working days after offerings are completed. Additionally, the Trial Measures stipulate that after an issuer has offered and listed securities in an overseas market, the issuer shall submit a report to the CSRC within three working days after the occurrence and public disclosure of (i) a change of control thereof, (ii) investigations of or sanctions imposed on the issuer by overseas securities regulators or relevant competent authorities, (iii) changes of listing status or transfers of listing segment, and (iv) a voluntary or mandatory delisting.

The CSRC Filing Notice states that, beginning from March 31, 2023, PRC domestic enterprises which have already issued and listed securities overseas and fall within the scope of filing under the Trial Measures shall be considered "existing enterprises" ("Existing Listed Enterprises"). Existing Listed Enterprises are not required to complete filings immediately; rather, Existing Listed Enterprises should complete filings if they are subsequently involved in matters require filings, such as follow-on financing activities, in accordance with the Trial Measures.

Regulations on Foreign Exchange and Dividend Distribution

Foreign Exchange Control

According to the PRC Regulation for the Foreign Exchange promulgated by the State Council in January 1996, which was amended in January 1997 and August 2008, and the Regulation on the Administration of the Foreign Exchange Settlement, Sales and Payment promulgated by the People's Bank of China in June 1996, foreign exchanges required for distribution of profits and payment of dividends may be purchased from designated foreign exchange banks in the PRC upon presentation of a board resolution authorizing distribution of profits or payment of dividends.

According to the Circular of the State Administration of Foreign Exchange, or the SAFE, on Further Improving and Adjusting the Foreign Exchange Policies on Direct Investment and its appendix promulgated in November 2012 and amended in May 2015, October 2018 and December 2019 by the SAFE, (1) the opening of and payment into foreign exchange accounts under direct investment accounts are no longer subject to approval by the SAFE; (2) reinvestment with legal income of foreign investors in China is no longer subject to approval by SAFE; (3) the procedures for capital verification and confirmation that foreign-funded enterprises need to go through are simplified; (4) purchase and external payment of foreign exchange under direct investment accounts are no longer subject to approval by SAFE; (5) domestic transfer of foreign exchange under direct investment account is no longer subject to approval by SAFE; and (6) the administration over the conversion of foreign exchange capital of foreign-invested enterprises is improved. Later, the SAFE promulgated the Circular on Further Simplifying and Improving Foreign Exchange Administration Policies in Respect of Direct Investment in February 2015, which was further amended in December 2019 and prescribed that the bank instead of the SAFE can directly handle the foreign exchange registration and approval under foreign direct investment while the SAFE and its branches indirectly supervise the foreign exchange registration and approval under foreign direct investment through the bank.

The Provisions on the Administration of Foreign Exchange in Foreign Direct Investments by Foreign Investors, which were promulgated by the SAFE in May 2013 and amended in October 2018 and December 2019, regulate and clarify the administration over foreign exchange administration in foreign direct investments.

According to the Circular on the Reform of the Management Method for the Settlement of Foreign Exchange Capital of Foreign-invested Enterprises promulgated by the SAFE in Mach 2015 and amended in December 2019, and the Circular on the Reform and Standardization of the Management Policy of the Settlement of Capital Projects promulgated by the SAFE in June 2016, the settlement of foreign exchange by foreign invested enterprises shall be governed by the policy of foreign exchange settlement on a discretionary basis. However, the settlement of foreign exchange shall only be used for their own operational purposes within the business scope of the foreign invested enterprises and follow the principles of authenticity.

Dividend Distribution

The SAFE promulgated the Notice on Improving the Check of Authenticity and Compliance to Further Promote Foreign Exchange Control in January 2017, which stipulates several capital control measures with respect to outbound remittance of profits from domestic entities to offshore entities, including the following: (1) under the principle of genuine transaction, banks shall check board resolutions regarding profit distribution, the original version of tax filing records and audited financial statements; and (2) domestic entities shall hold income to account for previous years' losses before remitting the profits. Moreover, domestic entities shall make detailed explanations of sources of capital and utilization arrangements, and provide board resolutions, contracts and other proof when completing the registration procedures in connection with an outbound investment.

Foreign Exchange Registration of Offshore Investment by PRC Residents

The SAFE promulgated the SAFE Circular 37 in July 2014. The SAFE Circular 37 requires PRC residents (including PRC institutions and individuals) to register with local branches of SAFE in connection with their direct or indirect offshore investment in an overseas special purpose vehicle, or the SPV, directly established or indirectly controlled by PRC residents for offshore investment and financing with their legally owned assets or interests in domestic enterprises, or their legally owned offshore assets or interests. Such PRC residents are also required to amend their registrations with the SAFE when there is a change to the basic information of the SPV, such as changes of a PRC resident individual shareholder, the name or operating period of the SPV, or when there is a significant change to the SPV, such as changes of the PRC individual resident's increase or decrease of its capital contribution in the SPV, or any share transfer or exchange, merger, division of the SPV.

The Circular on Further Simplifying and Improving Foreign Exchange Administration Policies in Respect of Direct Investment, which was promulgated in February 2015 and effective in June 2015 and further amended in December 2019, provides that PRC residents may register with qualified banks instead of the SAFE in connection with their establishment or control of an offshore entity established for the purpose of overseas direct investment. The SAFE and its branches shall implement indirect supervision over foreign exchange registration of direct investment via the banks.

Failure to comply with the registration procedures set forth in the SAFE Circular 37 may result in restrictions on the foreign exchange activities of the relevant onshore company, including the payment of dividends and other distributions to its offshore parent or affiliate, the capital inflow from the offshore entities and settlement of foreign exchange capital, and may also subject relevant onshore company or PRC residents to penalties under PRC foreign exchange administration regulations.

Regulations on Labor

Labor Law and Labor Contract Law

According to the PRC Labor Law, which was promulgated by the Standing Committee of the NPC in July 1994 and amended in August 2009 and December 2018, respectively, the PRC Labor Contract Law, which was promulgated by the Standing Committee of the NPC in June 2007 and amended in December 2012 and came into effect July 2013, and the Implementing Regulations of the Employment Contracts Law of the PRC, which was promulgated by the State Council in September 2008, labor contracts in written form shall be executed to establish labor relationships between employers and employees. In addition, wages cannot be lower than the local minimum wage. The employers must establish a system for labor safety and sanitation, strictly abide by State rules and standards, provide education regarding labor safety and sanitation to its employees, provide employees with labor safety and sanitation conditions and necessary protection materials in compliance with State rules, and carry out regular health examinations for employees engaged in work involving occupational hazards.

Social Insurance and Housing Provident Funds

According to the Social Insurance Law of PRC, which was promulgated by the Standing Committee of the NPC in October 2010 and came into effect in July 2011, and further amended in December 2018, and the Interim Regulations on the Collection and Payment of Social Security Funds, which was promulgated by the State Council in January 1999 and amended in March 2019, and the Regulations on the Administration of Housing Provident Funds, which was promulgated by the State

Council in April 1999 and amended in March 2002 and March 2019, employers are required to contribute, on behalf of their employees, to a number of social security funds, including funds for basic pension insurance, unemployment insurance, basic medical insurance, occupational injury insurance, maternity insurance and to housing provident funds. Any employer who fails to contribute may be fined and ordered to make good the deficit within a stipulated time limit.

Regulations on Taxation

Enterprise Income Tax

According to the Enterprise Income Tax Law promulgated by the Standing Committee of the NPC in March 2007 and amended in February 2017 and December 2018, and the Implementation Rules of the Enterprise Income Tax Law of the PRC promulgated by the State Council in December 2007 and amended in April 2019, other than a few exceptions, the income tax rate for both domestic enterprises and foreign-invested enterprises is 25%. Enterprises are classified as either "resident enterprises" or "non-resident enterprises." Besides enterprises established within the PRC, enterprises established outside China whose "de facto management bodies" are located in China are considered "resident enterprises" and subject to the uniform 25% enterprise income tax rate for their global income. A non-resident enterprise refers to an entity established under foreign law whose "de facto management bodies" are not within the PRC but which have an establishment or place of business in the PRC, or which do not have an establishment or place of business in the PRC but have income sourced within the PRC. An income tax rate of 10% will normally be applicable to dividends declared to non-PRC resident enterprise investors that do not have an establishment or place of business in the PRC, or that have such establishment or place of business but the relevant income is not effectively connected with the establishment or place of business, to the extent such dividends are derived from sources within the PRC.

According to the Notice on Promoting the Implementation of Corporate Income Tax Policies for Advanced Technology Service Enterprises Nationwide, or the Notice, since January 2017, an enterprise which is recognized as an "Advanced Technology Service Enterprises" under the Notice enjoys a reduced enterprise income tax rate of 15%.

According to the Arrangement Between the Mainland of China and the Hong Kong Special Administrative Region for the Avoidance of Double Taxation and Prevention of Fiscal Evasion with Respect to Taxes on Income, or the Double Tax Avoidance Arrangement, which was promulgated and came into effect in August 2006, and other applicable PRC laws, if a Hong Kong resident enterprise is determined by the competent PRC tax authority to have satisfied the relevant conditions and requirements under such Double Tax Avoidance Arrangement and other applicable laws, the 10% withholding tax on the dividends the Hong Kong resident enterprise receives from a PRC resident enterprise may be reduced to 5%. However, based on the Circular on Certain Issues with Respect to the Enforcement of Dividend Provisions in Tax Treaties which was promulgated by the State Administration of Taxation, the STA, in February 2009, if the relevant PRC tax authorities determine, in their discretion, that a company benefits from such reduced income tax rate due to a structure or arrangement that is primarily tax-driven, such PRC tax authorities may adjust the preferential tax treatment. Based on the Announcement on Certain Issues with Respect to the "Beneficial Owner" in Tax Treaties, which was promulgated by the STA in February 2018 and came into effect in April 2018, if an applicant's business activities do not constitute substantive business activities, it could result in the negative determination of the applicant's status as a "beneficial owner," and consequently, the applicant could be precluded from enjoying the above-mentioned reduced income tax rate of 5% under the Double Tax Avoidance Arrangement.

Value Added Tax

According to the Provisional Regulations of the PRC on Value-Added Tax, effective in January 1994 and further amended in November 2008, February 2016, and November 2017, and its implementation rules effected in January 1994 and amended in December 2008 and October 2011, except stipulated otherwise, taxpayers who sell goods, labor services or tangible personal property leasing services or import goods shall be subject to a 17% tax rate; taxpayers who sell transport services, postal services, basic telecommunications services, construction services, or real property leasing services, sell real property, transfer the land use right shall be subject to an 11% tax rate, and taxpayers who sell services or intangible assets shall be subject to a 6% tax rate.

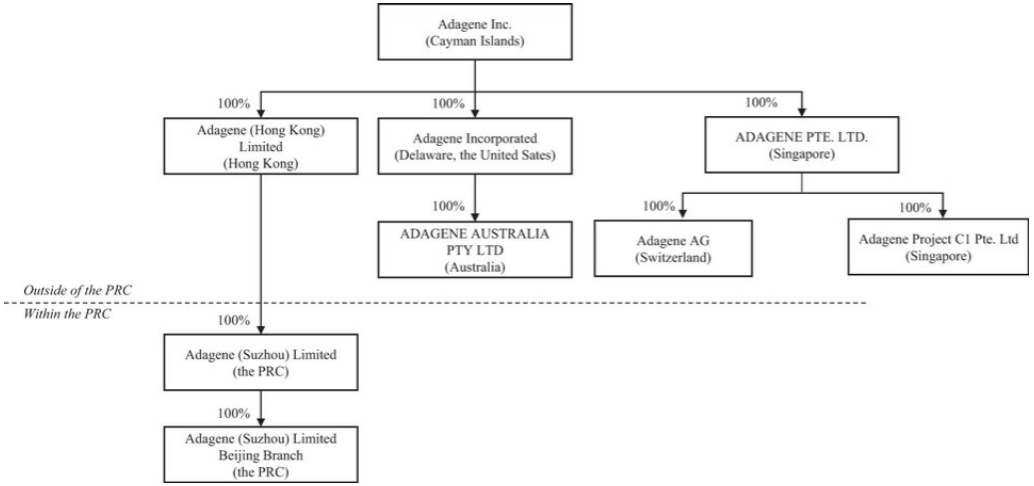
According to the Circular of the Ministry of Finance and the State Administration of Taxation on Adjusting Value-added Tax Rates adopted in April 2018, as of May 2018, where a taxpayer engages in a taxable sales activity for the value-added tax purpose or imports goods, the previous applicable 17% and 11% rates are adjusted to 16% and 10%.

According to the Announcement on Relevant Policies for Deepening Value-Added Tax Reform, effective in April 2019, the 16% VAT tax rate, which applies to the sales or imported goods of a VAT general taxpayer, will be lowered to 13%; and the 10% VAT tax rate will be lowered to 9%.

According to the Measures for the Exemption of Value-Added Tax from Cross-Border Taxable Activities in the Collection of Value-Added Tax in Lieu of Business Tax (for Trial Implementation) revised in June 2018, if domestic enterprises provide cross-border taxable activities such as professional technical services, technology transfer, software services, the above-mentioned cross-border taxable activities are exempt from VAT.

4.C. Organizational Structure

The following diagram illustrates our corporate structure as of the date of this annual report, including our material subsidiaries directly or indirectly owned by us through equity ownership (our group structure does not include any variable interest entities):



4.D. Property, Plants and Equipment

Our headquarter is based in Suzhou, China, which are approximately 2,946 square meters in size. The expiration dates of the lease agreements for this facility range from March 31, 2023 to September 15, 2024. We also have a 1,081 square feet facility in San Diego, California for laboratory, research and development functions, the lease for which expires on August 31, 2023. We do not expect difficulties in renewing lease agreements for our facilities.

ITEM 4A. UNRESOLVED STAFF COMMENTS

None.

ITEM 5. OPERATING AND FINANCIAL REVIEW AND PROSPECTS

You should read the following discussion and analysis of our financial condition and results of operations in conjunction with the section entitled "Selected Consolidated Financial Data" and our consolidated financial statements and the related notes included elsewhere in this annual report. This discussion contains forward-looking statements that involve risks and uncertainties. Our actual results and the timing of events could differ materially from those anticipated in these forward-looking statements as a result of various factors, including those we describe under "Item 3.D. Risk Factors" and elsewhere in this annual report.

5.A. Operating Results

We are a platform-driven, clinical-stage biotechnology company transforming the discovery and development of novel antibody-based cancer immunotherapies. We are combining computational biology and artificial intelligence to design novel antibodies that address unmet patient needs. Powered by our proprietary Dynamic Precision Library (DPL) platform, which fuels our NEObody™, SAFEbody®, and POWERbody™ technologies, we are developing a highly differentiated pipeline of novel immunotherapies. We have forged strategic collaborations with reputable global partners that leverage our technology in multiple approaches at the vanguard of science.

We aim to push the boundaries of antibody discovery and engineering through the precise design, construction, and selection of antibody product candidates intractable to traditional antibody technology. We have pioneered a dynamic antibody technology interface to harness the conformational diversity of antibodies, which enlarges epitope sampling of a given drug target for differentiated therapeutic antibody development. Additionally, we have a proprietary precision masking technology and specialized antibody engineering capabilities which enable us to design therapeutics with unique features.

Our Dynamic Precision Library fuels our three antibody technology platforms, which can be used alone or together to create novel, differentiated antibody-based therapeutic candidates. By leveraging our proprietary DPL platform and three platform technologies, we have developed a robust pipeline of innovative product candidates in various stages of development, ranging from research and discovery to preclinical and clinical development. Our highly differentiated and wholly-owned clinical-stage pipeline consists of two anti-CTLA-4 antibodies ADG116 (NEObody) and ADG126 (SAFEbody), and two anti-CD137 antibodies ADG106 (NEObody) and ADG206 (POWERbody). ADG116, ADG126 and ADG106 are in Phase 1b/2 clinical evaluation in single agent and/or combination clinical trials designed to evaluate safety and preliminary efficacy, while ADG206 is in Phase 1 single agent clinical trial. We also have a robust preclinical pipeline of four programs in IND-enabling studies, including a masked anti-CD47 SAFEbody, as well as over 50 programs in various stages of discovery.

Since our inception in 2011, our operations have focused on organizing and staffing our company, conducting preclinical studies and clinical trials, business planning, establishing our intellectual property portfolio and raising capital. We do not have any product candidates approved for sale and have not generated any revenue from product sales. We have financed operations mainly through the private placements of our preferred shares before our initial public offering completed in February 2021 and through proceeds received from the initial public offering.

Since inception, we have incurred significant operating losses. Our net losses were US$42.4, US$73.2 million and US$80.0 million for the years ended December 31, 2020, 2021 and 2022, respectively. As of December 31, 2022, we had accumulated deficit of US$258.8 million. We expect to continue to incur significant expenses and operating losses for the foreseeable future. We anticipate that our expenses will increase significantly in connection with our ongoing activities, as we:

- continue advancement of and investment in our proprietary DPL platform;
- advance the development of ADG116, ADG126, ADG106, ADG206 and other preclinical drug candidates;
- continue our ongoing and planned research and development of other lead product candidates;
- discover and develop additional antibody product candidates and further expand our preclinical and clinical product pipeline;
- maintain, expand and protect our intellectual property portfolio;

- expand our collaborations with contract manufacturing organizations and contract research organizations;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- establish sales and marketing teams and distribution network to commercialize any product candidate for which we may obtain regulatory approval;
- attract, hire and retain additional clinical, scientific, management and administrative personnel;
- expand our operations globally; and
- incur additional costs associated with operating as a public company.

Beginning in January 2020, the emergence and wide spread of COVID-19 has resulted in quarantines, travel restrictions, and the temporary closure of stores and facilities in the United States and China and elsewhere. Substantially all of our operating and workforce are based in the United States and China. Since late July 2021, the delta variant of COVID-19 has resurged in several provinces across China and the Omicron variant of COVID-19 has been detected in most states and territories of the United States and is rapidly increasing the proportion of COVID-19 cases it is causing. Consequently, the COVID-19 outbreak and its resurgences caused by the new variants could potentially delay a patient's access to hospital and the progress of our clinical trials, including patient enrollment, which may adversely affect our business operations, financial condition and operating results for 2023.

The extent of the impact of the COVID-19 pandemic on our business, operations and regulatory and commercialization timelines will depend on certain developments, including the duration and spread of the outbreak and its impact on clinical trials, regulatory authorities and our key scientific and management personnel as well as its impact on our partners, laboratory sites, and other third parties with whom we collaborate, and the extent of future resurgences of the disease and its variants, vaccine distribution and other actions in response to the virus or to contain its impact, and we are closely monitoring its impact on us. See "Item 3 Key Information—Risk Factors—Risks relating to obtaining regulatory approval of our drug candidates—The COVID-19 pandemic could adversely impact our business, including our clinical trials." We will continue to actively monitor the rapidly evolving situation related to COVID-19 and may take further actions that alter our business operations, including those that may be required by government authorities, or that we determine are in the best interests of our employees, partners and shareholders. At this point, the extent to which the COVID-19 pandemic may impact our business, operations and regulatory and commercialization timelines remains uncertain.

Key Components of Results of Operations

Revenue

Licensing and collaboration revenue. Our licensing and collaboration revenue is currently comprised of upfront and/or milestone payments associated with out-licensing arrangements. Our licensing and collaboration revenue for the years ended December 31, 2020, 2021 and 2022 was primarily derived from granting licenses to use and otherwise exploit certain of our intellectual properties. To date, we have not generated any revenue from the sale of products and do not expect to generate any revenue from product sales in the near future.

Expenses

Research and Development Expenses. Our research and development expenses consist principally of (1) payroll and other related costs of personnel engaged in research and development activities, (2) costs related to pre-clinical testing of our technologies under development and clinical trials such as payments to contract research organizations, or CRO, and contract manufacturing organization, or CMO, investigators and clinical trial sites that conduct the clinical studies, (3) costs to develop the product candidates, including raw materials and supplies, product testing, depreciation and amortization, and facility related expenses, and (4) other research and development expenses.

For the years ended December 31, 2020, 2021 and 2022, our research and development expenses were US$33.5 million, US$68.1 million and US$81.3 million, respectively. The increase was primarily due to increased research and development activities for our clinical programs and preclinical testing for candidates in the IND-enabling phase.

Our research and development expenses may vary substantially from period to period according to the status of our research and development activities. The timing of expenses is impacted by the commencement of clinical trials and enrollment of patients in clinical trials. Research and development expenses are expected to increase as we advance the clinical development of ADG116, ADG126, ADG106 and ADG206, and further advance the research and development of our other product candidates. The successful development of our product candidates is uncertain.

The following table summarizes our research and development expenses for our clinical-stage product candidates, preclinical product candidates and research pipeline for the years ended December 31, 2020, 2021 and 2022, respectively.

	For the Year Ended December 31,		
	2020	2021	2022
	US$	US$	US$
		(in thousands)	
ADG126	12,091	3,543	19,229
ADG116	3,156	11,236	15,271
ADG106	12,504	14,798	4,604
Preclinical product candidates, research pipeline and others	5,787	38,522	42,236
Total	**33,538**	**68,099**	**81,340**

At this time, we cannot reasonably estimate the nature, timing and estimated costs of the efforts that will be necessary to complete the development of, or the period, if any, in which material net cash inflows may commence from, any of our product candidates. This is due to numerous risks and uncertainties associated with developing drugs, including the uncertainty of:

- the scope, rate of progress, results and cost of our clinical trials, preclinical studies and other related activities;
- the cost of manufacturing clinical supplies, and establishing commercial supplies, of any product candidates;
- the number and characteristics of product candidates that we pursue;
- the cost, timing and outcomes of regulatory approvals;
- the cost and timing of establishing sales, marketing and distribution capabilities; and
- the terms and timing of any collaboration, licensing or other arrangements that we may establish, including any required milestone and royalty payments thereunder.

A change in the outcome of any of these variables with respect to the development of our product candidates or any other current or future product candidates could mean a significant change in the costs and timing associated with the development of such product candidate. For example, if we are required to conduct additional clinical trials or other testing of any of our product candidates beyond those that are contemplated or if we experience significant delays in enrollment in any clinical trials, we could incur significant additional costs and the clinical development timeline for our product candidates may be delayed.

Administrative expenses . . Our administrative expenses consist primarily of wages, salaries and benefits for personnel other than research and development staff. Our administrative expenses, excluding share-based compensation expenses, may decrease in absolute amount in the year ended December 31, 2023 as we implement different cost control measures.

Other income

Other income primarily includes government subsidies that Adagene Suzhou received from local government in the PRC. The receipt of such government subsidies is not dependent on our performance of any obligations. In addition, the subsidiary in Australia received research and development tax incentive from the Australian Taxation Office. The tax incentive was recognized as other income upon receipt as the incentive was not dependent upon having a tax liability and further performance by the Group was not required.

Taxation

Cayman Islands

We are incorporated in the Cayman Islands. Under the current laws of the Cayman Islands, we are not subject to income, corporation or capital gains tax in the Cayman Islands. In addition, our payment of dividends, if any, is not subject to withholding tax in the Cayman Islands.

Hong Kong

Our wholly-owned subsidiary in Hong Kong, Adagene (Hong Kong) Limited, is subject to Hong Kong profits tax on the taxable income as reported in its statutory financial statements adjusted in accordance with the relevant Hong Kong tax laws. The applicable tax rate in Hong Kong is 16.5%. Under Hong Kong tax law, our subsidiary in Hong Kong is exempted from income tax on their foreign-derived income and there is no withholding tax in Hong Kong on remittance of dividends. No provision for Hong Kong profits tax was made as there were no assessable profits derived from or earnings in Hong Kong for the years ended December 31, 2020, 2021 and 2022.

United States

Our subsidiary in the U.S., Adagene Incorporated, is incorporated in the U.S. and subject to U.S. federal corporate income tax at a rate of 21%. It is also subject to state income tax in California of 8.84%. Dividends payable by an U.S. entity, to non-U.S. resident enterprises shall be subject to 30% withholding tax, unless the respective non-U.S. resident enterprise’s jurisdiction of incorporation has a tax treaty or arrangements with U.S. that provides for a reduced withholding tax rate or an exemption from withholding tax.

PRC

Our subsidiary in China is incorporated under PRC law and, as such, is subject to PRC enterprise income tax on their taxable income in accordance with the relevant PRC income tax laws. Pursuant to the PRC Enterprise Income Tax Law, or EIT Law, which became effective on January 1, 2008, a uniform 25% enterprise income tax rate is generally applicable to both foreign-invested enterprises and domestic enterprises, except where a special preferential rate applies. In accordance with the implementation rules of EIT Law, a qualified Technology Advanced Service Enterprises, or TASE, is eligible for a preferential tax rate of 15%. The TASE certificate is effective for three years. An entity must file required supporting documents with the tax authority and ensure fulfillment of the relevant TASE criteria before using the preferential rate. An entity could apply for the TASE certificate every year. Adagene Suzhou was first recognized as a qualified TASE in March 2015 and renewed in December 2018 and December 2021. Adagene Suzhou can enjoy the preferential tax rate of 15% from 2015 to at least 2023. In addition, the research and development expenses of Adagene Suzhou are subject to a 75% super-deduction for the income tax, which increased to 100% from October 2022 to December 2022. The enterprise income tax is calculated based on the entity’s global income as determined under PRC tax laws and accounting standards.

We are subject to VAT at a rate of 3%, 6%, or 13% on the services we provide and related surcharges. We are also subject to surcharges on VAT payments in accordance with PRC law.

As a Cayman Islands holding company, we may receive dividends from Adagene Suzhou. The PRC EIT Law and its implementing rules provide that dividends paid by a PRC entity to a nonresident enterprise for income tax purposes is subject to PRC withholding tax at a rate of 10%, subject to reduction by an applicable tax treaty with China. Pursuant to the Arrangement between Mainland China and the Hong Kong Special Administrative Region for the Avoidance of Double Taxation and Tax Evasion on Income, the withholding tax rate in respect to the payment of dividends by a PRC enterprise to a Hong Kong enterprise may be reduced to 5% from a standard rate of 10% if the Hong Kong enterprise directly holds at least 25% of the PRC enterprise. Pursuant to the Notice of the State Administration of Taxation on the Issues concerning the Application of the Dividend Clauses of Tax Agreements, or SAT Circular 81, a Hong Kong resident enterprise must meet the following conditions, among others, in order to apply the reduced withholding tax rate: (i) it must be a company; (ii) it must directly own the required percentage of equity interests and voting rights in the PRC resident enterprise; and (iii) it must have directly owned such required percentage in the PRC resident enterprise throughout the 12 months prior to receiving the dividends. In August 2015, the State Administration of Taxation promulgated the Administrative Measures for Nonresident Taxpayers to Enjoy Treatment under Tax Treaties, or SAT Circular 35, which later became effective on January 1, 2020. SAT Circular 35 provides that non-resident enterprises are not required to obtain pre-approval from the relevant tax authority in order to enjoy the reduced withholding tax. Instead, nonresident enterprises and their withholding agents may, by self-assessment and on confirmation that the prescribed criteria to enjoy the tax treaty benefits are met, directly apply the reduced withholding tax rate, and file necessary forms and supporting documents when performing tax filings, which will be subject to post-tax filing examinations by the relevant tax authorities. Accordingly, Adagene (Hong Kong) Limited may be able to benefit from the 5% withholding tax rate for the dividends it receives from its PRC subsidiary, if it satisfies the conditions prescribed under SAT Circular 81 and other relevant tax rules and regulations. However, according to SAT Circular 81 and SAT Circular 35, if the relevant tax authorities consider the transactions or arrangements we have are for the primary purpose of enjoying a favorable tax treatment, the relevant tax authorities may adjust the favorable withholding tax in the future.

If our holding company in the Cayman Islands or any of our subsidiaries outside of China were deemed to be a “resident enterprise” under the PRC EIT Law, it would be subject to enterprise income tax on its worldwide income at a rate of 25%. See “Item 3 Key Information— Risk Factors—Risks Related to Doing Business in the PRC—If we are classified as a PRC resident enterprise for PRC income tax purposes, such classification could result in unfavorable tax consequences to us and our non-PRC shareholders or ADS holders.”

Critical Accounting Policies and Judgments

Basis of presentation

Our consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP.

Principles of Consolidation

Our consolidated financial statements include the financial statements of Adagene Inc. and its subsidiaries. All significant intercompany balances and transactions have been eliminated upon consolidation.

Use of estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosures of contingent assets and liabilities at the balance sheet dates and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in our consolidated financial statements include, but are not limited to, licensing and collaboration revenue recognition, research and development expense allocation, the useful lives and impairment of long-lived assets, tax valuation allowance, share-based compensation expenses and measurement of right-of-use assets and lease liabilities. Management bases the estimates on historical experience and various other assumptions that are believed to be reasonable, the results of which form the basis for making judgments about the carrying values of assets and liabilities. Actual results could materially differ from those estimates.

Foreign currency translation

The functional currency of Adagene Inc., Adagene (Hong Kong) Limited, Adagene Incorporated, Adagene PTE. Ltd. and Adagene Project C1 PTE. Ltd. is the U.S. dollar, or US$. The functional currency of our PRC subsidiary is Renminbi, or RMB. The functional currency of our Australia subsidiary is Australian dollar, or AU$.The functional currency of our Swiss subsidiary is Swiss Franc, or CHF. The determination of the respective functional currency is based on the criteria stated in Accounting Standard Codification, or ASC, 830, *Foreign Currency Matters*. We use US$ as our reporting currency. The financial statements of our PRC subsidiary, Australia subsidiary and Swiss subsidiary are translated from the functional currency to the reporting currency.

Transactions denominated in foreign currencies are re-measured into the functional currency at the exchange rates quoted by the People's Bank of China, or the PBOC, prevailing on the transaction dates. Monetary assets and liabilities denominated in foreign currencies are re-measured at the exchange rates prevailing at the balance sheet date. Non-monetary items that are measured in terms of historical costs in foreign currency are re-measured using the exchange rates at the dates of the initial transactions. Exchange gains and losses are included in the consolidated statements of comprehensive loss.

Assets and liabilities are translated at the exchange rates at the balance sheet date, equity accounts are translated at historical exchange rates and revenues, expenses, gains and losses are translated using the average rate for the year. Translation adjustments are reported as accumulated comprehensive loss and are shown as a separate component of other comprehensive loss in the consolidated statements of comprehensive loss.

Revenue recognition

At contract inception of collaboration and out-licensing arrangement, we analyze the arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements*, or ASC 808, to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are reflective of a vendor-customer relationship and therefore within the scope of ASC 606, *Revenue from Contracts with Customers*, or ASC 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently.

Under the criteria of ASC 606, we recognize revenue to depict the transfer of control of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to receive in exchange for those goods or services. We adopted ASC 606 for all periods presented. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. We only apply the five-step model to contracts when it is probable that the entity will collect substantially all the consideration to which it is entitled in exchange for the goods or services it transfers to the customer. We review the contract to determine which performance are distinct and represent a promise to provide distinct goods or services or a series of distinct goods or services as defined by the standard. We recognize as revenue the amount of the transaction price that is allocated to each performance obligation as and when that performance obligation is satisfied.

Licenses of Intellectual Property: Upfront non-refundable payments for licensing our intellectual property are evaluated to determine if the license is distinct from the other performance obligations identified in the arrangement. For licenses determined to be distinct, we recognize revenues from non-refundable, up-front fees allocated to the license at a point in time, when the transfer of control of the license to the licensee occurs and the licensee is able to use and benefit from the license. For licenses determined not to be distinct, we account for the promise to grant a license and those other promised goods or services together as a single performance obligation when recognizing revenue.

Research and Development Services: The portion of the transaction price allocated to research and development services performance obligations is deferred and recognized over time as delivery of such services occurs.

Milestone Payments: At the inception of each arrangement that includes development, commercialization, and regulatory milestone payments, we evaluate whether the milestones are considered probable of being reached and to the extent that a significant reversal of cumulative revenue would not occur in future periods, estimates the amount to be included in the transaction price using the most likely amount method. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability of achieving such development milestones and any related constraint, and if necessary, adjust the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Contract assets and contract liabilities: When a customer pays consideration before we transfer products or services, we record our obligation as a contract liability; when we satisfy our performance obligations by providing products or services to a customer before the customer pays consideration and before payment is due, we recognize our rights to consideration as a contract asset.

Fair value measurements

We apply ASC 820, *Fair Value Measurements and Disclosures*, or ASC 820. ASC 820 defines fair value, establishes a framework for measuring fair value and expands disclosures about fair value measurements. ASC 820 requires disclosures to be provided for fair value measurements. ASC 820 establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value as follows:

Level 1—Observable inputs that reflect quoted prices (unadjusted) for identical assets or liabilities in active markets.

Level 2—Other inputs that are directly or indirectly observable in the marketplace.

Level 3—Unobservable inputs which are supported by little or no market activity.

ASC 820 describes three main approaches to measuring the fair value of assets and liabilities: (1) market approach; (2) income approach; and (3) cost approach. The market approach uses prices and other relevant information generated from market transactions involving identical or comparable assets or liabilities. The income approach uses valuation techniques to convert future amounts to a single present value amount. The measurement is based on the value indicated by current market expectations about those future amounts. The cost approach is based on the amount that would currently be required to replace an asset.

The carrying amounts of cash and cash equivalent, short-term investments, accounts receivable, amounts due to related parties and other current assets, accounts payable, amounts due to related parties, accrued liabilities and other current liabilities and short-term borrowings approximate their fair values because of their generally short maturities. The carrying amount of long-term borrowings approximate their fair values since they bear interest rates which approximate market interest rates.

We did not transfer any assets or liabilities in or out of Level 3 during the year ended December 31, 2021 or 2022.

We had no financial assets and liabilities measured and recorded at fair value on a nonrecurring basis as of December 31, 2021 and 2022.

Research and development expenses

Elements of research and development expenses primarily include (1) payroll and other related costs of personnel engaged in research and development activities, (2) costs related to pre-clinical testing of our technologies under development and clinical trials such as payments to contract research organizations, or CRO, and contract manufacturing organizations, or CMO, investigators and clinical trial sites that conduct the clinical studies; (3) costs to develop the product candidates, including raw materials and supplies, product testing, depreciation and amortization, and facility related expenses, (4) other research and development expenses. Research and development expenses are charged to expense as incurred when these expenditures relate to our research and development services and have no alternative future uses. As of December 31, 2022, we have several ongoing clinical studies in various clinical trial stages. The contracts with CRO and CMO are generally cancellable, with notice, at our option. We did not record any accrued expenses related to cancellation of CRO or CMO contracts as of December 31, 2021 or 2022 as we did not have any plan to cancel the existing CRO or CMO contracts.

Income taxes

We follow the liability method of accounting for income taxes in accordance with ASC 740, *Income Taxes*, or ASC 740. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial reporting and tax bases of assets and liabilities using enacted tax rates that will be in effect in the period in which the differences are expected to reverse. We record a valuation allowance to offset deferred tax assets if based on the weight of available evidence, it is more likely than not that some portion, or all, of the deferred tax assets will not be realized. The effect on deferred taxes of a change in tax rate is recognized in tax expense in the period that includes the enactment date of the change in tax rate.

We evaluate our uncertain tax positions using the provisions of ASC 740, which prescribes a recognition threshold that a tax position is required to meet before being recognized in the consolidated financial statements.

We recognize in the consolidated financial statements the benefit of a tax position which is “more likely than not” to be sustained under examination based solely on the technical merits of the position assuming a review by tax authorities having all relevant information. Tax positions that meet the recognition threshold are measured using a cumulative probability approach, at the largest amount of tax benefit that has a greater than fifty percent likelihood of being realized upon settlement. It is our policy to recognize interest and penalties related to unrecognized tax benefits, if any, as a component of income tax expense.

We have incurred net accumulated operating losses for income tax purposes since our inception. We believe that it is more likely than not that these net accumulated operating losses will not be utilized in the near future. Therefore, we have provided full valuation allowances for the deferred tax assets for subsidiaries other than the U.S. subsidiary as of December 31, 2021 and for all subsidiaries as of December 31, 2022. There was no income tax expense for the years ended December 31, 2020, as our subsidiaries did not have any taxable profits. For the year ended December 31, 2021 and 2022, income tax expense was US$1.7 and US$0.5 million due to taxable profits generated by the U.S. subsidiary, respectively.

Share-based compensation

We grant restricted shares and stock options to eligible employees and nonemployees and accounts for share-based compensation in accordance with ASC 718, Compensation—Stock Compensation.

Share-based compensation awards are measured at the grant date fair value of the awards and recognized as expenses a) immediately at the grant date if no vesting conditions are required; or b) for share-based awards granted with only service conditions, using the straight-line method over the vesting period; or c) for share-based awards granted with service conditions and performance conditions, using the graded vesting method over the vesting period if and when the company concludes that it is probable that the performance conditions will be achieved.

A change in any of the terms or conditions of share-based awards is accounted for as a modification of the awards. We calculate incremental compensation expense of a modification as the excess of the fair value of the modified awards over the fair value of the original awards immediately before its terms are modified at the modification date. For vested awards, we recognize incremental compensation cost in the period when the modification occurs. For awards not being fully vested, we recognize the sum of the incremental compensation expense and the remaining unrecognized compensation expense for the original awards over the remaining requisite service period after modification.

The fair value of share options was determined using the binomial option valuation model, with the assistance from an independent third-party appraiser. The binomial model requires the input of highly subjective assumptions, including the expected volatility, the exercise multiple, the risk-free rate and the dividend yield. For expected volatility, we have made reference to historical volatility of several comparable companies in the same industry. The exercise multiple was estimated as the average ratio of the stock price to the exercise price of when employees would decide to voluntarily exercise their vested share options. The risk-free rate for periods within the contractual life of the share options is based on the market yield of U.S. Treasury Bonds in effect at the time of grant. The dividend yield is based on the expected dividend policy over the contractual life of the share options. Our management is ultimately responsible for the determination of the estimated fair value of its ordinary shares.

The assumptions used to estimate the fair value of the share options granted are as follows:

	For the year eneded December 31,		
	2020	**2021**	**2022**
Risk-free interest rate	0.68% - 0.83 %	1.11% - 1.67 %	1.92% - 4.25 %
Dividend yield	0 %	0 %	0 %
Expected volatility range	72.3% - 73.4 %	73.1% - 75.5 %	74.2% - 74.9 %
Exercise multiple	2.2 - 2.8	2.2 - 2.8	2.2 - 2.8
Contractual life	10 years	10 years	10 years

Borrowings

Borrowings are recognized initially at fair value, net of transaction costs incurred. Borrowings are subsequently stated at amortized cost; any difference between the proceeds (net of transaction costs) and the redemption value is recognized in the consolidated statements of comprehensive loss over the period of the borrowings using the effective interest method.

Recent accounting pronouncements

A list of recent relevant accounting pronouncements is included in Note 2 “Summary of Significant Accounting Policies” to our consolidated financial statements included elsewhere in this annual report.

Results of Operations

The following table summarizes our consolidated results of operations for the periods presented. This information should be read together with our consolidated financial statements and related notes included elsewhere in this annual report. The operating results in any period are not necessarily indicative of the results that may be expected for any future period.

	For the Year Ended December 31,		
	2020	2021	2022
	US$	US$	US$
	(in thousands, except per share information)		
Revenue:			
Licensing and collaboration revenue	701	10,175	9,293
Expenses:			
Research and development expenses	(33,538)	(68,099)	(81,340)
Administrative expenses	(10,315)	(14,440)	(11,874)
Total operating expenses	**(43,853)**	**(82,539)**	**(93,214)**
Loss from operations	**(43,152)**	**(72,364)**	**(83,921)**
Interest income	629	76	378
Interest expense	(202)	(364)	(693)
Other income, net	972	1,779	2,168
Foreign exchange gain (loss), net	(645)	(603)	2,555
Loss before income tax	**(42,397)**	**(71,476)**	**(79,513)**
Income tax expense	—	(1,702)	(459)
Net loss attributable to Adagene Inc.'s shareholders	**(42,397)**	**(73,178)**	**(79,972)**
Other comprehensive income (loss):			
Foreign currency translation adjustments, net of nil tax	(6)	257	(755)
Total comprehensive loss attributable to Adagene Inc.'s shareholders	**(42,403)**	**(72,921)**	**(80,727)**
Net loss attributable to Adagene Inc.'s shareholders	**(42,397)**	**(73,178)**	**(79,972)**
Accretion of convertible redeemable preferred shares to redemption value	(248)	(28)	—
Net loss attributable to ordinary shareholders	**(42,645)**	**(73,206)**	**(79,972)**
Weighted average number of ordinary shares used in per share calculation:			
—Basic	15,951	50,032	54,135
—Diluted	15,951	50,032	54,135
Net loss per ordinary share			
—Basic	(2.67)	(1.46)	(1.48)
—Diluted	(2.67)	(1.46)	(1.48)

Year Ended December 31, 2022 Compared to Year Ended December 31, 2021

Licensing and collaboration revenue

Our licensing and collaboration revenue was US$9.3 million for the year ended December 31, 2022, compared to US$10.2 million for the year ended December 31, 2021. Our licensing and collaboration revenue in 2022 was recognized due to fulfillment of performance obligations over time associated with the collaboration and technology licensing agreement with Sanofi to develop antibody-based therapies. Such revenue was also recognized from the material transfer and option agreement with ADCT as performance obligation was satisfied at a point in time in 2022.

Research and development expenses

The following table sets forth a breakdown of the major components of our research and development expenses in absolute amounts and as a percentage of our total research and development expenses for the periods indicated:

	For the Year Ended December 31,			
	2021		2022	
	US$	%	US$	%
	(in thousands, except percentages)			
Research and development expenses				
Payroll and other related costs of personnel	28,293	41.5 %	24,093	29.6 %
Costs related to clinical programs	15,278	22.4 %	29,384	36.2 %
Costs related to clinical trials	8,371	12.3 %	14,277	17.6 %
CMC and toxicology costs associated with the clinical programs	6,907	10.1 %	15,107	18.6 %
Costs related to preclinical testing of non-clinical programs	16,795	24.7 %	20,697	25.4 %
Costs required to develop the product candidates	3,103	4.6 %	2,216	2.7 %
Other research and development expenses	4,630	6.8 %	4,950	6.1 %
Total	68,099	100 %	81,340	100 %

Our research and development expenses increased by 19.4% from US$68.1 million for the year ended December 31, 2021 to US$81.3 million for the year ended December 31, 2022, primarily attributable to increased research and development activities for our clinical programs and preclinical testing for candidates in the IND-enabling phase.

Administrative expenses

Our administrative expenses decreased by 17.4% from US$14.4 million for the year ended December 31, 2021 to US$11.9 million for the year ended December 31, 2022, primarily attributable to a decrease in personnel expenses of US$2.1 million, and a decrease in professional fees and office-related expenses of US$0.4 million.

Loss from operations

As a result of the foregoing, our loss from operations increased by 15.9% from approximately US$72.4 million in the year ended December 31, 2021 to approximately US$83.9 million in 2022.

Interest income

Our interest income was US$0.4 million for the year ended December 31, 2022, as compared to US$0.1 million for the year ended December 31, 2021. This increase was primarily attributable to an increase in interest rate and increase in the amount of term deposits placed.

Other income

Our other income increased from US$1.8 million for the year ended December 31, 2021 to US$2.2 million for the year ended December 31, 2022, primarily attributable to (i) an increase in government subsidies received by Adagene Suzhou to support our ongoing operations in Jiangsu Province during the year ended December 31, 2022, and (ii) a research and development tax incentive from the Australian Taxation Office received by Adagene Australia Pty Ltd, our wholly-owned subsidiary in Australia.

Foreign exchange loss, net

We recorded foreign exchange loss of US$0.6 million for the year ended December 31, 2021 and foreign exchange gain of US$2.6 million for the year ended December 31, 2022. This gain of foreign exchange was primarily attributable to the appreciation of U.S. dollars against Renminbi which positively impacted our U.S. dollar denominated accounts receivable of Adagene Suzhou.

Income tax expense

Our income tax expense was US$1.7 million for the year ended December 31, 2021 as compared to US$0.5 million for the year ended December 31, 2022. The income tax expense for the year ended December 31, 2022 was primarily attributable to the current tax expenses on income reported by Adagene Incorporated, our wholly owned subsidiary in the U.S.

Net loss attributable to Adagene Inc.'s shareholders

Our net loss for the period increased by 9.3% from US$73.2 million for the year ended December 31, 2021 to US$80.0 million for the year ended December 31, 2022. The 2022 net loss was higher largely due to increases in costs associated with clinical, pre-clinical and CMC activities.

Year Ended December 31, 2021 Compared to Year Ended December 31, 2020

See “Item 5. Operating and Financial Review and Prospects – 5.A Operating Results —Year Ended December 31, 2021 Compared to Year Ended December 31, 2020” beginning on page 166 of our annual report on Form 20-F for the year ended December 31, 2021 filed with the Securities and Exchange Commission on April 26, 2021 incorporated by reference into this annual report.

Non-GAAP Financial Measures

Non-GAAP net loss, which is defined as net loss attributable to ordinary shareholders for the period after excluding (i) share-based compensation expenses and (ii) accretion of convertible redeemable preferred shares to redemption value, as applicable. The Non-GAAP net loss was US$69.5 million for the year ended December 31, 2022, compared to US$54.5 million for the same period in 2021. Non-GAAP net loss per ordinary share for the year ended December 31, 2022 on both basic and diluted basis was US$1.28. Non-GAAP net loss per ordinary share for the year ended December 31, 2021 on both basic and diluted basis was US$1.09.

We use non-GAAP net loss and non-GAAP net loss per ordinary share for the year, which are non-GAAP financial measures, in evaluating our operating results and for financial and operational decision-making purposes. We believe that non-GAAP net loss and non-GAAP net loss per ordinary share for the year help identify underlying trends in our business that could otherwise be distorted by the effect of certain expenses that we include in our loss for the year. We believe that non-GAAP net loss and non-GAAP net loss per ordinary share for the year provide useful information about our results of operations, enhance the overall understanding of its past performance and future prospects and allow for greater visibility with respect to key metrics used by its management in our financial and operational decision-making.

Non-GAAP net loss and non-GAAP net loss per ordinary share for the year should not be considered in isolation or construed as an alternative to operating profit, loss for the year or any other measure of performance or as an indicator of its operating performance. Investors are encouraged to review non-GAAP net loss and non-GAAP net loss per ordinary share for the year and the reconciliation to their most directly comparable GAAP measures. Non-GAAP net loss and non-GAAP net loss per ordinary share for the year here may not be comparable to similarly titled measures presented by other companies. Other companies may calculate similarly titled measures differently, limiting their usefulness as comparative measures to our data. We encoruage investors and others to review our financial information in its entirety and not rely on a single financial measure.

Non-GAAP net loss and non-GAAP net loss per ordinary share for the year represent net loss attributable to ordinary shareholders for the year excluding (i) share-based compensation expenses, and (ii) accretion of convertible redeemable preferred shares to redemption value.

Please see the "Reconciliation of GAAP and Non-GAAP Results" below for a full reconciliation of GAAP net loss attributable to ordinary shareholders for the year to non-GAAP net loss attributable to ordinary shareholders and non-GAAP net loss per ordinary share for the year.

Reconciliation of GAAP and Non-GAAP Results

	For the years ended December 31,		
	2020	**2021**	**2022**
	US$	**US$**	**US$**
GAAP net loss attributable to ordinary shareholders	**(42,645,392)**	**(73,206,488)**	**(79,971,847)**
Add back:			
Share-based compensation expense	10,129,541	18,679,658	10,520,282
Accretion of convertible redeemable preferred shares to redemption value	248,113	28,553	—
Non-GAAP net loss attributable to ordinary shareholders	**(32,267,738)**	**(54,498,277)**	**(69,451,565)**
Weighted average number of ordinary shares used in per share calculation:			
—Basic	15,950,698	50,032,009	54,135,084
—Diluted	15,950,698	50,032,009	54,135,084
Non-GAAP net loss per ordinary share			
—Basic	(2.02)	(1.09)	(1.28)
—Diluted	(2.02)	(1.09)	(1.28)

5.B. Liquidity and Capital Resources

Since the inception, we have incurred net losses and negative cash flow from our operations. We do not expect to generate any revenue from product sales unless and until we obtain regulatory approval and subsequently commercialize one of our current or future drug candidates. We expect to incur additional operating losses in the near future and our operating expenses will increase as we continue to expand our research and development capabilities, invest in preclinical tests and clinical trials and increase our efforts in obtaining regulatory approvals. In addition, subject to obtaining regulatory approval of any of our product candidates, we expect to incur significant commercialization expenses for product sales, marketing and manufacturing. Moreover, we expect to incur additional costs associated with operating as a public company, including expenses related to legal, accounting, regulatory, maintaining compliance with exchange listing and SEC requirements, director and officer insurance premiums, and investor relations.

Our principal source of liquidity has been cash generated from the proceeds received from the issuance and sale of our shares. In February 2021, we completed our initial public offering in which we issued and sold an aggregate of 8,457,100 ADSs, representing 10,571,375 ordinary shares, resulting in net proceeds to us of approximately US$145.9 million, net of the underwriting discounts and commissions and other fees paid or payable by us in connection with the offering. As of December 31, 2022, we had US$143.8 million in cash and cash equivalents.

We intend to finance our future working capital requirements and capital expenditures primarily from funds raised from financing activities, including the net proceeds received from our initial public offering, future public and private offerings of our securities, proceeds from our collaborations, and/or proceeds from borrowings.

Based on our current operating plan, we believe that our current cash and cash equivalents will be sufficient to meet our current and anticipated working capital requirements and capital expenditures for at least the next 12 months.The assumptions on which our estimates are based may prove to be wrong, and we may use our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amount of increased capital outlays and operating expenditures necessary to complete the development and commercialization of our product candidates.

In utilizing the proceeds that we received from our initial public offering, we may make capital contributions to our subsidiaries in the PRC, the United States, Australia, Hong Kong, Singapore and Switzerland, acquire or establish new subsidiaries, or grant loans to our subsidiaries. However, uses of the proceeds by our PRC subsidiary are subject to PRC regulations. See “Item 3 Key Information—Risk Factors—Risks Related to Doing Business in China—PRC regulation of loans to and direct investment in PRC entities by offshore holding companies and governmental control of currency conversion may delay or prevent us from using the proceeds of our initial public offering to make loans or additional capital contributions to our PRC subsidiary, which could materially and adversely affect our liquidity and our ability to fund and expand our business.” We have operations in China and many of the related transactions are settled in Renminbi. Our financial statements are presented in U.S. dollars. Under existing PRC foreign exchange regulations, Renminbi may be converted into foreign currencies for current account items, including profit distributions, interest payments and trade- and service-related foreign exchange transactions, without prior SAFE approval as long as certain routine procedural requirements are fulfilled. Our PRC subsidiary is allowed to pay dividends in foreign currencies to us without prior SAFE approval by following certain routine procedural requirements. However, approval from or registration with competent government authorities is required where the Renminbi is to be converted into foreign currency and remitted out of China to pay capital expenses such as the repayment of loans denominated in foreign currencies. The PRC government may at its discretion restrict access to foreign currencies for current account transactions in the future.

The following table presents our selected consolidated cash flow data for the years ended December 31, 2020, 2021 and 2022.

	For the Year Ended December 31,		
	2020	2021	2022
	US$	US$	US$
		(in thousands)	
Net cash used in operating activities	(28,530)	(43,415)	(48,612)
Net cash (used in) generated from investing activities	7,073	(2,510)	(686)
Net cash generated from financing activities	4,439	145,357	17,823
Effect of exchange rate on cash and cash equivalents	(364)	(192)	843
Net increase (decrease) in cash and cash equivalents	(17,382)	99,240	(30,632)
Cash and cash equivalents at the beginning of year	92,533	75,151	174,391
Cash and cash equivalents at the end of year	**75,151**	**174,391**	**143,759**

Operating activities

Net cash used in operating activities was US$48.6 million in 2022. The difference between our net loss of US$80.0 million and the net cash used in operating activities was mainly due to (i) an increase in prepayments and other current assets of US$0.9 million, (ii) a decrease in accruals and other current liabilities of US$0.8 million, (iii) a decrease in income tax payable of US$1.7 million as income tax was paid, and (iv) a decrease in lease liabilities of US$0.3 million given adoption of ASC 842, offset by (i) non-cash share-based compensation expenses of US$10.5 million, (ii) a decrease of accounts receivable of US$3.0 million given receipt of milestone payment from Exelixis, Inc., (iii) a decrease in amounts due from related parties of US$3.9 million, (iv) an increase of accounts payable of US$0.3 million, (v) an increase in contract liabilities of US$9.6 million given receipt of upfront fee from Sanofi, (vi) an increase in amount due to related parties of US$8.9 million, (vii) depreciation and amortization of US$1.1 million, and (viii) amortization of right-of use assets and interest of lease liabilities of US$0.3 million.

Net cash used in operating activities was US$43.4 million in 2021. The difference between our net loss of US$73.2 million and the net cash used in operating activities was mainly due to (i) an increase of accounts receivable of US$3.0 million due to milestone payment from Exelixis, Inc. which was received in January 2022, (ii) an increase in prepayments and other current assets of US$0.2 million due to our prepaid service fees to our vendors, and (iii) an increase in amount due from related parties of US$4.4 million due to prepayments made to our related parties, offset by (i) non-cash share-based compensation expenses of US$18.7 million, (ii) an increase in accounts payable of US$1.5 million, (iii) an increase in contract liabilities of US$4.8 million, (iv) an increase in amount due to related parties of US$7.9 million, (v) an increase in accruals and other current liabilities of US$1.1 million, (vi) an increase in income tax payable of US$1.7 million, and (vii) depreciation and amortization of US$1.1 million.

Net cash used in operating activities was US$28.5 million in 2020. The difference between our net loss of US$42.4 million and the net cash used in operating activities was mainly due to (i) an increase in prepayments and other current assets of US$2.3 million due to our prepaid service fees to our vendor, (ii) a decrease in contract liabilities of US$0.3 million, offset by (i) non-cash share-based compensation expenses of US$10.1 million, (ii) an increase in accounts payable of US$1.1 million (iii) a decrease in accounts receivable of US$0.5 million, (iv) a decrease in amount due from related parties of US$1.3 million, (v) an increase in accruals and other current liabilities of US$1.2 million, and (vi) depreciation and amortization of US$0.9 million.

Investing activities

Net cash used in investing activities was US$0.7 million in 2022, which was primarily attributable to the purchase of property, equipment and software.

Net cash used in investing activities was US$2.5 million in 2021, which was attributable to the purchase of property, equipment and software.

Net cash generated from investing activities was US$7.1 million in 2020, which was primarily attributable to withdrawal of short-term investments of US$8.0 million, partially offset by purchase of property, equipment and software of US$0.9 million.

Financing activities

Net cash generated from financing activities was US$17.8 million in 2022, which was mainly attributable to proceeds from borrowings of US$25.8 million, offset by (i) repayment of borrowings of US$4.4 million, and (ii) purchase of treasury shares under stock repurchase program of US$4.0 million.

Net cash generated from financing activities was US$145.4 million in 2021, which was mainly attributable to (i) proceeds from initial public offering net of underwriting commissions of $149.4 million, and (ii) proceeds from borrowings of US$4.4 million, offset by (i) repayment of borrowings of US$5.1 million, (ii) payment of initial public offering costs of US$1.6 million, and (iii) purchase of treasury shares under stock repurchase program of US$2.4 million.

Net cash generated from financing activities was US$4.4 million in 2020, which was mainly attributable to proceeds from borrowings of US$6.1 million, partially offset by repayment of borrowings of US$1.1 million.

Capital Expenditures

Our capital expenditures are incurred primarily in connection with research and development equipment. Our capital expenditures were US$0.9 million, US$2.5 million and US$0.7 million, in 2020, 2021 and 2022, respectively. We intend to fund our future capital expenditures with our existing cash balance. We will continue to incur capital expenditures to meet the expected growth of our business.

Holding Company Structure

Adagene Inc. is a holding company with no material operations of its own. Adagene Inc. holds certain intellectual properties and outsources certain research and development activities related to these intellectual properties to its subsidiaries. We conduct our operations primarily through our subsidiaries. As a result, our ability to pay dividends depends upon dividends paid by our subsidiaries. If our subsidiaries or any newly formed subsidiaries incur debt on their own behalf in the future, the instruments governing their debt may restrict their ability to pay dividends to us.

In addition, our subsidiary in China is permitted to pay dividends to us only out of their retained earnings, if any, as determined in accordance with the Accounting Standards for Business Enterprise as promulgated by the Ministry of Finance of the PRC, or PRC GAAP. Pursuant to the law applicable to China's foreign investment enterprise, our subsidiary that is foreign investment enterprise in the PRC has to make appropriation from its after-tax profit, as determined under PRC GAAP, to reserve funds including (i) general reserve fund, (ii) enterprise expansion fund and (iii) staff bonus and welfare fund. The appropriation to the general reserve fund must be at least 10% of the after-tax profits calculated in accordance with PRC GAAP. Appropriation is not required if the reserve fund has reached 50% of the registered capital of our subsidiary. Appropriation to the other two reserve funds are at our subsidiary's discretion.

As an offshore holding company, we are permitted under PRC laws and regulations to provide funding from the proceeds of our offshore fund-raising activities to our PRC subsidiary through loans or capital contribution, subject to the satisfaction of the applicable government registration and approval requirements. See "Item 3 Key Information— Risk Factors—Risks Related to Doing Business in the PRC—PRC regulation of loans to and direct investment in PRC entities by offshore holding companies and governmental control of currency conversion may delay or prevent us from using the proceeds of our initial public offering to make loans or additional capital contributions to our PRC subsidiary, which could materially and adversely affect our liquidity and our ability to fund and expand our business." As a result, there is uncertainty with respect to our ability to provide prompt financial support to our PRC subsidiary when needed.

5.C. Research and Development, Patents and Licenses, Etc.

See "Item 4 Information on the Company—4.C. Business Overview — Our Platform" and "—Intellectual Property."

5.D. Trend Information

Other than as disclosed elsewhere in this annual report, we are not aware of any trends, uncertainties, demands, commitments or events for the year ended December 31, 2022 that are reasonably likely to have a material and adverse effect on our net revenues, income, profitability, liquidity or capital resources, or that would cause the disclosed financial information to be not necessarily indicative of future results of operations or financial condition.

5.E. Critical Accounting Estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosures of contingent assets and liabilities at the balance sheet dates and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in the Group's consolidated financial statements include, but are not limited to, licensing and collaboration revenue recognition, research and development expense allocation, the useful lives and impairment of long-lived assets, tax valuation allowance, share based compensation expenses, and measurement of right-of-use assets and lease liabilities. Management bases the estimates on historical experience and various other assumptions that are believed to be reasonable, the results of which form the basis for making judgments about the carrying values of assets and liabilities. Actual results could materially differ from those estimates.

Certain of these estimates are considered critical as they involve a significant level of estimation uncertainty and have had or are reasonably likely to have a material impact on our consolidated financial statements. Our critical accounting estimates are summarized below. See Note 2 to our consolidated financial statements included elsewhere in this annual report for a description of our significant accounting policies.

Revenue recognition

We adopted ASC 606 for all periods presented. Consistent with the criteria of ASC 606, we recognize revenue to depict the transfer of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to receive in exchange for those goods or services.

Our collaborative arrangements may contain more than one unit of account, or performance obligation, including grants of licenses to intellectual property rights, agreement to provide research and development services and other deliverables. The collaborative arrangements do not include a right of return for any deliverable. As part of the accounting for these arrangements, we must develop assumptions that require judgment to determine the stand-alone selling price based on contractual price and other factors for each performance obligation identified in the contract. In general, the consideration allocated to each performance obligation is recognized when the respective obligation is satisfied either by delivering a good or providing a service, limited to the consideration that is not constrained.

At the inception of each arrangement that includes development milestone payments, we evaluate whether the milestones are considered probable of being reached and to the extent that a significant reversal of cumulative revenue would not occur in future periods, estimates the amount to be included in the transaction price using the most likely amount method based on the nature and preconditions of the development milestones. There are uncertainties in terms of the judgement over the probability of achieving such development milestones and any related constraint. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability of achieving such development milestones and any related constraint, and if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Changes in assumptions or estimates can materially affect the revenue recognized. The assessment and conclusion reached for revenue recognition are disclosed in note 10 to our consolidated financial statements included elsewhere in this annual report.

Research and Development Expenses

Research and development expenses are charged to expense as incurred when these expenditures relate to our research and development services and have no alternative future uses.

Preclinical and clinical trial costs are a significant component of our research and development expenses. We have a history of contracting with third parties that perform various preclinical and clinical trial activities on behalf of us during the ongoing research and development process. Expenses related to preclinical and clinical trials are accrued based on our estimates of the actual services performed by the third parties for the respective period.

The process of estimating our research and development expenses involves reviewing open contracts and purchase orders, communicating with our research and development personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated costs incurred for the services when we have not yet been invoiced or otherwise notified of the actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting expenses that are too high or too low in any particular period. To date, we have not made any material adjustments to our prior estimates of research and development expenses.

Share based compensation

Share-based compensation awards are measured at the grant date fair value of the awards and recognized as expenses a) immediately at the grant date if no vesting conditions are required; b) for share-based awards granted with only service conditions, using the straight-line method over the vesting period; or c) for share-based awards granted with service conditions and performance conditions, using the graded vesting method over the vesting period if and when the we conclude that it is probable that the performance conditions will be achieved.

Estimating fair value for share-based payment transactions requires determination of the most appropriate valuation model, which depends on the terms and conditions of the grant. This estimate also requires determination of the most appropriate inputs to the valuation model including expected volatility, the exercise multiple, the risk free rate and the dividend yield and making assumptions about them. The cost related to share based compensation is sensitive to the aforementioned inputs. These inputs are evaluated periodically considering historical actuals and management judgement. For the measurement of the fair value of share options at the grant date, we use a binomial option valuation model. Changes in assumptions or estimates can materially affect the fair value of the share-based compensation awards. The assumptions and models used for estimating fair value for share-based payment transactions are disclosed in Note 9 to our consolidated financial statements included elsewhere in this annual report.

Deferred tax assets

In accordance with the provisions of ASC 740, *Income Taxes*, we recognize in our financial statements the benefit of a tax position if the tax position is more likely than not to prevail based on the facts and technical merits of the position.

Judgement is required to determine whether deferred tax assets are recognized in the statement of financial position. Deferred tax assets arise because of temporary differences between the financial reporting and tax basis of assets and liabilities, as well as from net operating losses. A valuation allowance is provided to reduce the amount of deferred tax assets if it is considered more likely than not that some portion or all of the deferred tax assets will not be realized in the foreseeable future. In making such determination, we evaluate a variety of positive and negative factors including our operating history, accumulated deficit, the existence of taxable temporary differences and reversal periods. However, the ultimate realization of our deferred tax assets is subject to a number of variables, including our future profitability within relevant tax jurisdictions. The actual benefits ultimately realized may differ from our estimates. The assessment of the deferred tax assets as well as related valuation allowance is disclosed in note 11 to our consolidated financial statements included elsewhere in this annual report.

ITEM 6. DIRECTORS, SENIOR MANAGEMENT AND EMPLOYEES

6.A. Directors and Senior Management

The following table sets forth information regarding our executive officers, key employees and directors as of the date of this annual report.

Executive Officers	Position/Title
Peter Luo, Ph.D	Co-Founder, Chief Executive Officer and Chairman of the Board
Fangyong (Felix) Du, Ph.D	Chief Technology Officer and Director
JC Xu, M.D., Ph.D	Chief Scientific Officer
Qinghai Zhao, Ph.D	Chief Manufacturing Officer
Man Kin (Raymond) Tam, M.B.A., B. Eng.	Chief Financial Officer and Director
Chunfang (Vicky) Gu M.B.A	Senior Director of Finance
Ling (Jolin) Zhou	Executive Director of Human Resources

Key Employees	Position/Title
Yan Li, M.B.A.	Senior Vice President, Bioinformatics and Information Technology
Xiaohong (Kristine) She	Senior Vice President, Head of Clinical Operations
Guizhong Liu, Ph.D.	Head of Biology and Pharmacology
Alexander Goergen	Vice President, Head of Business Development
Songmao Zheng, Ph.D.	Vice President, Head of Clinical and Quantitative Pharmacology
Jiping Zha	Executive Vice President of Clinical Development
Wenlin Zeng	Vice President of Early Stage CMC
Ami Knoefler	Vice President of Investor Relations and Corporate Communications
Dana Hu-Lowe	Vice President of Global Product Team Leadership
Ai Li	Vice President, Head of Biometrics

Non-Employee Directors	Position/Title
Yumeng Wang	Director
Andy (Yiu Leung) Cheung	Independent Director
Min Li	Independent Director
Yuwen Liu*	Independent Director
Cuong Do	Independent Director
Mervyn Turner, Ph.D.	Independent Director

* The expiry of initial term of our independent director Yuwen Liu has been extended from February 2023 to April 2023. Upon the filing of our annual report for the year ended Decemebr 31, 2022, the extended initial term of Ms. Liu's directorship will expire and Ms. Liu will depart from the Board and audit committee of the Board. Ms. Liu has confirmed that she has no disagreement with the Board.

Executive Officers

Peter Luo, Ph.D. is our Co-Founder and has served as our Chief Executive Officer since November 2011 and Chairman of the Board of the Directors since February 2018. Dr. Luo served as the first lead scientist in computational protein design and protein laboratory at Xencor (Nasdaq: XNCR) from July 1998 to August 2000. In September 2000, Dr. Luo founded Abmaxis Inc. and served as its Co-Founder, Chief Technology Officer, president, and director. In May 2006, Dr. Luo led the acquisition of Abmaxis Inc. by Merck & Co. (NYSE: MRK), after which Dr. Luo served as a director of Biologics Technology at Merck, and Chief Technology Officer of Abmaxis, the subsidiary of Merck & Co. Throughout his career, Dr. Luo also led the business development efforts in connection with collaborations and strategic partnerships with multiple global partners. Dr. Luo received his bachelor's degree in applied chemistry in technical physics from Peking University in 1986, master's degree in applied physics from The Institute of High Energy Physics of the Chinese Academy of Sciences in 1989, and Ph.D. degree in chemistry from The University of Chicago in 1995. Dr. Luo also completed his postdoctoral research in protein folding at Stanford University in 1998. Dr. Luo's spouse is Xiaohong (Kristine) She who is our Senior Vice President, Head of Clinical Operations.

Fangyong (Felix) Du, Ph.D. joined us as Vice President of Technology Development in January 2012 and has served as our Chief Technology Officer since May 2019 and our director since April 2023. Dr. Du has over 20 years of experience in biological research and discovery, and has published numerous peer-reviewed articles in world-renowned scientific journals such as Nature and Science. Dr. Du worked at Affomix from October 2009 to July 2010 and Illumina (Nasdaq: ILMN) from July 2010 to January 2012, and then joined the Company in January 2012 as the Vice President of Technology Development. Dr. Du received his bachelor's degree and master's degree in physiology and biophysics in 1991 and 1994, respectively, from Peking University, and his Ph.D. degree in biology from the California Institute of Technology in 2001. Dr. Du also completed his postdoctoral research from Yale University in 2007.

JC Xu, M.D., Ph.D. has served as our Chief Scientific Officer since August 2020. Dr. Xu has more than 20 years of experience in oncology drug discovery and development, and more than four years of experience in business development, strategy, and operations in the biopharmaceutical industry in the United States. Prior to joining Adagene, Dr. Xu was head of R&ED China Strategy at Celgene now BMS from 2017 to 2020. Prior to that, Dr. Xu was Director of Strategy & Operations at Celgene Quanticel Research and Director of Biology at Quanticel Pharmaceuticals from 2012 to 2017. Prior to Quanticel, Dr. Xu worked in leadership roles at a number of biopharmaceutical companies, including Pfizer, Amgen, and Corixa.

Dr. Xu received her M.D. degree from Beijing Medical University (now Peking University Health Science Center) in 1987 and her Ph.D. degree in Immunology from University of Alabama at Birmingham in 1993. She completed her post-doctoral training at DNAX Research Institute (now Merck Palo Alto) in 1996. She is an inventor of more than 120 issued and pending patents and has published more than 50 articles in peer-reviewed journals.

Qinghai Zhao, Ph.D. has served as our Chief Manufacturing Officer since October 2020. Dr. Zhao has more than 25 years of experience in protein therapeutics development and defining product development strategy from early stage IND through commercial filing. Prior to joining Adagene, Dr. Zhao was Vice President of Technical Development and Manufacturing at Forty Seven Inc. (NASDAQ:FTSV) from 2017 to October 2020. Prior to that, Dr. Zhao was vice president of CMC/ Manufacturing at AnaptysBio (NASDAQ:ANAB) from 2016 to 2017. Prior to AnaptysBio, Dr. Zhao worked as an Executive Director and the Head of CMC at NGM Biopharmaceuticals from 2014 to 2016. Dr. Zhao also held various positions at Human Genome Sciences, Inc., Cogenesys and Teva Biopharmaceuticals USA from 2001 to 2014. Dr. Zhao received his bachelor's degree from Shanghai Chemical Engineering Institute (now East China University of Sciences and Technology) in 1982, master's degree from Shanghai Medical University (now merged with Fudan University) in 1986 and Ph.D. degree from University of Uppsala in 1998.

Man Kin (Raymond) Tam has served as our Chief Financial Officer since September 2019 and our director since February 2021. Mr. Tam has over 20 years of management experience in finance and banking across the Asia-Pacific region. Mr. Tam worked in HSBC and J.P. Morgan Chase Bank, N.A. from 1999 to 2010. Mr. Tam served as project director of Mineralogy Pty Limited and Chief Financial Officer of Resourcehouse Limited from April 2010 to October 2015. From October 2015 to August 2019, Mr. Tam consecutively served as the Chief Financial Officer of China Regenerative Medicine International Limited (HKEx: 8158), Beijing Gas Blue Sky Holdings Limited (HKEx: 6828), and AgenTus Therapeutics, Inc. Mr. Tam is a fellow of CPA Australia, a member of the American Institute of Certified Public Accountants and the Hong Kong Institute of Certified Public Accountants. He is also a CFA and FRM charter-holder. He received his bachelor's degree in civil & resources engineering from the University of Auckland in 1997, master's degree in practising accounting from Monash University in 2001 and an Executive Master of Business Administration degree from the University of Western Ontario in 2005.

Chunfang (Vicky) Gu, M.B.A. joined Adagene in September 2017 and serves as Senior Director of Finance. Reporting to the Chief Financial Officer, Vicky manages Adagene Inc.'s finance team, plays a key role in Adagene Inc.'s capital markets and fund-raising transactions and assisted to establish the employee incentive plans of Adagene Inc. Vicky has over 17 years of experience in financial management with exposure to audit firms and multinational corporations including Sulzer Pumps, Bluescope Steel and Mercury Marine. Vicky has rich experience on financial reporting, budgeting and cost analysis, internal control and related compliance, taxation, as well as project management. Vicky received her Master of Business Administration degree from Xiamen University in 2016 and bachelor's degree in accounting from Tianjin University of Commerce in 2003. Vicky is a member of the American Institute of Certified Management Accountant.

Ling (Jolin) Zhou has served as our Executive Director of Human Resources since October 2019. Before joining Adagene, Ms. Zhou served as the HR director of Asia Pacific at Tekni-Plex, where she was responsible for strategic HR initiatives and business support from May 2010 to August 2019. Between October 2004 and May 2010, Ms. Zhou served as the HR supervisor at Suzhou Capsugel Ltd., a division of Pfizer, where she was responsible for all HR functions and personnel training. Ms. Zhou received her bachelor's degree in law from South-Central University for Nationalities in 2003. She is a DDI Certified Trainer.

Key Employees

Yan Li, M.B.A. has served as our Senior Vice President of Bioinformatics and Information Technology since November 2011. Ms. Li has over 25 years of experience in software development, with about 20 years focusing on the development of informatics software tools for antibody library design and analysis. Ms. Li served as the senior software engineer and applications scientist at Abmaxis from November 2001 to May 2006. Following the acquisition of Abmaxis by Merck & Co, Ms. Li worked at Merck & Co from May 2006 to December 2010. She received the Merck Award for Excellence in "Innovative Technologies" with the team and a Special Award for her contribution. Ms. Li received her bachelor's degree in information science from East China University of Science and Technology in 1995 and a Master of Business Administration degree in 2010 from Santa Clara University.

Xiaohong (Kristine) She has served as our Senior Vice President, Head of Clinical Operations since November 2011. Ms. She has over 20 years of laboratory and laboratory management experience in the renowned laboratories in the United States and has completed multiple projects in molecular biology and immunology at the labs of University of Chicago, the Genome Center at Stanford University, neurological animal studies at Stanford Palo Alto Veteran's Hospital, and cloning and functional screening of cDNA libraries at Caltech. Her work has been published in Nature, Science, Biotechnology, among many other notable publications. Ms. She received her bachelor's degree in microbiology from Wuhan University in 1986 and master's degree in biochemistry and microbiology from the Institute of Microbiology of the Chinese Academy of Sciences in 1989. Ms. She's spouse is Peter Luo, Ph.D., our Co-Founder, Chief Executive Officer and Chairman of the Board.

Guizhong Liu, Ph.D. has served as our Head of Biology and Pharmacology since October 2015. Dr. Liu has over 15 years of experience in drug discovery and development, both in small molecule kinase inhibitors and large molecule antibodies in oncology and immunology field. He has published over 40 peer-reviewed papers in high-profile journals involving key signalling pathways and targets in cancer biology. From July 2007 to August 2011, Dr. Liu served as an assistant professor of the department of oncological science at Mount Sinai School of Medicine. Prior to joining us, Dr. Liu served as head of molecular cancer biology in CrownBio from October 2011 to September 2015. Dr. Liu received his bachelor's degree in biology in 1992 and master's degree in cell biology in 1995 from Beijing Normal University and Ph.D. degree in cell biology from Peking Union Medical College in 1998. He also completed his postdoctoral training in cancer biology at Mount Sinai School of Medicine in 2004.

Alexander Goergen has served as our Head of Business Development since October 2017 when he joined the Company. Mr. Goergen has worked in various roles at the Covance, TRC and International AIDS Vaccine Initiative from October 2008 to October 2012. Prior to joining us, Alexander worked in business development for Catalent Pharma Solutions Biologics Division since October 2012. Mr. Goergen completed many licensing, manufacturing, and cell line development programs both domestically and internationally during his previous employment. Mr. Goergen received his bachelor's degree in Chemistry from Lafayette College in 2008 and master's degree in Biotechnology from the University of Wisconsin-Madison in 2011.

Songmao Zheng, Ph.D. is currently our Vice President, Head of Clinical and Quantitative Pharmacology, and leads quantitative model-informed drug discovery and development in both preclinical and clinical space. Prior to joining us, Dr. Zheng had served as Scientific Director/Group Leader, leading numerous biologics programs at Janssen BioTherapeutics, Janssen R&D since 2013. Dr. Zheng received his bachelor's degree in biological sciences from Sichuan University in 2007 and Ph.D. degree in pharmaceutical sciences from University of Washington in 2012.

Jiping Zha, Ph.D. has served as our Executive Vice President of Clinical Development since September 2021. Dr. Zha is responsible for clinical development, clinical operation and drug safety group. He is a physician scientist with over 20 years of formative experience in both academia and biotech industry. Dr. Zha has served as executive director of translational sciences at NGM Biopharmaceuticals from April 2017 to September 2021, and held various leadership positions at MedImmune, Crown Bioscience, Genentech from November 2003 to March 2017. Dr. Zha has over forty publications in high-impact scientific journals, such as Cell, Science and Nature, and authored multiple patents. Dr. Zha received his M.D. degree in basic medicine from Shanghai Medical University in 1987 and Ph.D. degree in Microbiology and Immunology from University of Tennessee in 1993, and was Board-Certified in Anatomic Pathology by American Board of Pathology in 1999.

Wenlin Zeng, Ph.D. has served as our Vice President of Early Stage CMC since June 2021. Dr. Zeng brings more than 20 years of experience in drug discovery and drug development in the biopharmaceutical industry. Prior to joining us, Dr. Zeng was the senior director of upstream process development responsible for both early and late stage programs at Gilead Sciences, Inc from July 2020 to June 2021. Prior to that, she was the senior director of cell line and upstream process development at Forty-Seven Inc. from April 2018 to June 2020, where she was responsible for cell line, upstream process development and manufacturing for a number of programs, including magrolimab. Prior to Forty-Seven, Dr. Zeng held leadership positions at multiple biopharmaceutical companies, including NGM Bio, GSK, MedImmune, and Abgenix. Dr. Zeng began her career in biopharmaceutical industry from June 1997 to April 2018 after completing her post-doctoral training at Stanford University. Dr. Zeng received her bachelor's degree in cell biology from Wuhan University in 1983 and Ph.D. degree in biochemistry from the Universy of Iowa in 1990.

Ami C. Knoefler has served as our Vice President of Investor Relations and Corporate Communications since July 2021. Ms. Knoefler has more than 25 years of global experience in pharmaceutical, biotech and medical technology communications. She most recently served as consultant and Senior Director at Ascendis Pharma from June 2015 to August 2021, and previously held multiple leadership positions at Jazz Pharmaceuticals, PDL BioPharma, Abgenix and Bristol-Myers Squibb from May 2007 to March 2013. She received her bachelor’s degree in mass communication/public relations from Boston University in 1992.

Dana Hu-Lowe, Ph.D. is currently our Vice President of Global Product Team Leadership. Dr. Hu-Lowe has more than 20 years of industry experience in oncology and R&D including years of experience in project and strategic alliance management, and leadership for both preclinical and clinical product programs. Before joining Adagene, she served as an Executive Director and Global Product Team Leader at Turning Point Therapeutics from April 2019 to October 2021. She was the Senior Director of Strategic Alliance and Program management at Wellspring Biosciences Inc. from March 2013 to March 2019, where she managed both internal discovery and IND-enabling programs and strategic alliance with Janssen Pharmaceuticals. Dr. Hu-Lowe had over 12 years of career at Pfizer Oncology November 1999 to December 2011, where she led cross-functional teams advancing programs from preclinical into clinical development. Dr. Hu-Lowe received her bachelor’s dgreee in chemistry from Beijing Normal University in 1984 and Ph.D. degree in biochemistry from the University of Mississippi in 1992 and completed her Post-doctoral training at Scripps Research Institute and the Burnham Cancer Center (now the Sanford Burnham Prebys Medical Discovery Institute).

Ai Li, Ph.D. has served as our Vice President, Head of Biometrics since March 2022. Dr. Li has over 14 years of experience as a biostatistician and lead of biometrics. Dr. Li has extensive experience in both early and late phase studies over various oncology indications. He has worked on small molecule and biologics drugs, T-cell therapy, and an oncolytic virus. He previously worked at QED Therapeutics (“QED”) FROM July 20220 to March 2022, leading the biometrics team for the filing of a targeted cancer therapy, which has been approved in the U.S., Canada, and Australia. Before QED, he worked for Novartis, Amgen, Puma Biotechnology and Atara Biotherapeutics, and was the key member of two successful NDA/BLA filings, including the first oncolytic virus approved for use in the U.S. and European Union. Dr. Li has more than 30 publications and received more than 3000 citations. Dr. Li received his bachelor’s degree in technical physics in 2000 and master’s degree in statistics in 2003 from Peking University. Dr. Li received his Ph.D. in Biostatistics from University of California, Los Angeles in 2007.

Non-Employee Directors

Yumeng Wang has served as our director since April 2023 designated by General Atlantic Singapore AI Pte. Ltd. pursuant to our current effective shareholders agreement. Ms. Yumeng Wang is currently a vice president at General Atlantic, primarily responsible for investments in healthcare and life sciences sectors. Prior to joining General Atlantic, Ms. Wang served as an equity research analyst at The Hongkong and Shanghai Banking Corporation, mainly focusing on the healthcare sector. Ms. Wang also serves as a non-executive director of Ocumension Therapeutics (1477.HK) and Biotheus Inc. Ms. Wang received her bachelor’s degree in business administration in June 2013 and her master degree in biotechnology in 2021 from The Hong Kong University of Science and Technology.

Andy (Yiu Leung) Cheung has served as our independent director since February 2021. Mr. Cheung has many years of auditing and accounting professional experience. Mr. Cheung was deputy area managing partner of Ernst & Young ("EY") in Asia Pacific overseeing the business operations, finance, information technology and risk management functions from July 2018 to June 2020. Mr. Cheung was the assurance leader for EY in Greater China from July 2013 to June 2018. Mr. Cheung has served as an independent non-executive director of JW (Cayman) Therapeutics Co. Ltd (HKEX:2126) since October 2020 and an independent non-executive director of Hua Medicine (HKEX:2552) since January 2023. Mr. Cheung received his bachelor's degree in accounting and finance from the University of Lancaster in the United Kingdom in July 1982. He obtained a master's degree in accounting and finance from London School of Economics and Political Science in the United Kingdom in August 1983. Mr. Cheung is a member of Hong Kong Institute of Certified Public Accountants.

Min Li, Ph.D. has served as our independent director since February 2021. Dr. Min Li is the founder, CEO and director of SciNeuro Pharmaceuticals, a biotechnology company headquartered in Shanghai focused on developing innovative therapeutics for CNS diseases. Dr. Li was formerly Senior Vice President, Global Head of Neuroscience R&D at GSK from 2013 to 2019. During his employment with GSK, he also served as General Manager of GSK R&D China, the highest-ranking officer at the country level. Before moving into industry, Dr. Li had served as a tenured Professor of Neuroscience at Johns Hopkins University School of Medicine for over 20 years. Dr. Li served on scientific advisory boards, non-profit and corporate boards that include multinational corporations (Corning, Pfizer and Merck), disease foundations (RYR-foundation, AHA) and biotech companies (Xencor, Affymax, Datavant, Icagen, and Coda Biotechnologies). He is also an Adjunct Professor of Neuroscience at Johns Hopkins School of Medicine. Dr. Li received his B.S. degree in biochemistry from Wuhan University in 1984 and his Ph.D. in molecular immunology from Johns Hopkins University in 1990. As a Helen Hay Whitney Fellow, he performed postdoctoral research at University of California San Francisco. With a Sloan Award, in 1994 he returned to Johns Hopkins to join the faculty as an Esther A & Joseph Klingenstein Neuroscience Fellow. Dr. Li has published more than 120 scientific articles and holds patents in biotechnologies. His research and scholarship were recognized internationally with awards including being a fellow of American Association for Advancement of Science and an established fellow of American Heart Association.

Yuwen Liu has served as our independent director since February 2022. Ms. Liu is a leading advocate for the biotechnology, biopharmaceutical and medical technology industries, with over 20 years as an entrepreneur, advisor and investor. From 2010 to 2014, Ms. Liu was Chair and CEO, followed by executive director, of Suzhou Industrial Park Biotech Development Co. Ltd. (BioBAY), building it into one of the fastest growing biotech clusters serving over 400 start-ups, including BrightGene, Innovent, and Qiagen (Suzhou), where she also served on the boards of directors. Prior to that, Ms. Liu served various positions at BioBay since 2005. As a strong supporter of innovation, she was also a founding partner of BOHE Angel Fund, one of the first angel funds in China focusing on healthcare start-ups, which invests in biologics, drug discovery and diagnostics. Ms. Liu was also a founding Chair of BioVENTURE Fund Investment committee. Ms. Liu previously served as the first Chief Representative to set up the China operation of Perrigo. Earlier in her career, she had various positions in quality and business development at Capsugel, a division of Warner-Lambert later acquired by Pfizer. Ms. Liu graduated from China Pharmaceutical University with a master's degree in pharmaceutics in 1997 and Master of Management at Fudan University and Norwegian Management School BI in 2004. She is a licensed pharmacist.

Cuong Do has served as our independent director since November 2022. Mr. Do is President and CEO of BioVie Inc., a clinical-stage company developing innovative therapies for Alzheimer's Disease, Parkinson's disease and refractory Ascites. Prior to BioVie, Mr. Do was President of Samsung's Global Strategy Group where he helped to set the strategic direction for Samsung Group's diverse business portfolio, including the growth of its biologics businesses. He was previously the Chief Strategy Officer for Merck, a leading global pharmaceuticals company, where he played a key role in defining the company's strategy, including the focus on oncology and creating its leading position with the anti-PD-1 therapy, pembrolizumab (KEYTRUDA®). Mr. Do was also a senior partner at McKinsey & Company, where he spent 17 years helping to build the healthcare, high technology, and corporate finance practices. He holds a BA from Dartmouth College and an MBA from the Tuck School of Business at Dartmouth.

Mervyn Turner, Ph.D., has served as our independent director since April 2023. Dr. Turner accumulated over 25 years of experience at Merck Research Laboratories in pharmaceuticals drug discovery, research and development, licensing and business development, emerging markets analysis, and strategy development and implementation. For seven years, he was head of world-wide licensing and external research at Merck, during a period of rapid expansion in Merck's partnering activities. He became Merck's first Chief Strategy Officer and a member of the senior executive team in 2008, before retiring from the company in 2011. Dr. Turner received his BS and Ph.D. in Chemistry from the University of Sheffield in 1970. He also completed his postdoctoral research in biochemistry of histocompatibility at Havard University in 1974.

6.B. Compensation

Compensation

For the fiscal year ended December 31, 2022, we paid an aggregate of US$3.7 million in cash to our executive officers and an aggregate of US$0.2 million in cash to our independent directors. For the fiscal year ended December 31, 2022, we did not pay any cash compensation to non-executive directors who are not independent directors. For the fiscal year ended December 31, 2022, we did not set aside or accrue expenses related to pension, retirement or other similar benefits to our executive officers and directors. Our PRC subsidiary is required by law to make contributions equal to certain percentages of each employee's salary for his or her pension insurance, medical insurance, unemployment insurance and other statutory benefits and a housing provident fund. For share incentive grants to our directors and executive officers, see "Item 6 Directors, Senior Management and Employees—Share Incentive Plan."

Employment Agreements and Indemnification Agreements

We have entered into employment agreements with each of our executive officers. Each of our executive officers is employed for a period of twelve months, which will be renewed automatically and extended automatically for a period of twelve months unless the executive or we give prior written notice. We may terminate an executive officer's employment for cause at any time without advance notice in certain events. We may terminate an executive officer's employment by giving a prior written notice or by paying certain compensation. In such case of termination by us, we will provide severance payments to the executive officer as expressly required by applicable law of the jurisdiction where the executive officer is based. An executive officer may terminate his or her employment at any time by giving a prior written notice.

Each executive officer has agreed to hold, unless expressly consented to by us, at all times during and after the termination of his or her employment agreement, in strict confidence and not to use, any of our confidential information or the confidential information of our customers and suppliers. In addition, each executive officer has agreed to be bound by certain non-competition and non-solicitation restrictions during the term of his or her employment and for a maximum of two years following the last date of employment.

We have entered into indemnification agreements with each of our directors and executive officers. Under these agreements, we agree to indemnify our directors and executive officers against certain liabilities and expenses incurred by such persons in connection with claims made by reason of their being a director or officer of our company.

Share Incentive Plan

Adagene Inc. Second Amended and Restated Share Incentive Plan

In November 2015, we adopted Adagene Inc. Share Incentive Plan, or the 2015 Plan, which was later superseded and replaced by Adagene Inc. Amended and Restated Share Incentive Plan, or the 2017 Plan, in September 2017. In December 2019, we adopted the Second Amended and Restated Share Incentive Plan, or the 2019 Plan, to supersede and replace the 2017 Plan. The terms of the 2015 Plan, the 2017 Plan and the 2019 Plan are substantially the same other than the maximum aggregate number of shares we may issue under the respective plan.

The purpose of the 2019 Plan is to attract, motivate, retain and reward certain officers, employees, directors and other eligible persons and to further link the interests of award recipients with those of our shareholders generally. The 2019 Plan provides for the issuance of up to an aggregate of 11,391,131 of our ordinary shares. We have terminated the authority to grant additional awards under the 2019 Plan and all future awards will be granted under the 2021 Plan. Therefore, the effective maximum number of shares issuable under the 2019 Plan is 10,125,726. As of March 31, 2023, the aggregate number of our ordinary shares underlying our outstanding awards under the 2019 Plan is 2,714,814, excluding awards that were forfeited, cancelled or exercised after the relevant grant dates. The term of the awards will expire not more than ten years after the date of grant.

The following paragraphs summarize the principal terms of the 2019 Plan.

Types of Awards. The 2019 Plan permits the awards of options, share appreciation rights, ordinary shares or restricted shares.

Plan Administration. The 2019 Plan shall be administrated by our board of directors or one or more committees appointed by the board of directors or another committee (within its delegated authority), the Plan Administrator.

Promissory Notes. The promissory notes with respect to the 2019 Plan, or the 2019 Promissory Notes are full recourse, repayable within a period of time determined by the Plan Administrator, which should not exceed five years (subject to certain early repayment events), and bear interest at the interest rate determined by the Plan Administrator but not less than the interest rate necessary to avoid the imputation of interest under United States Internal Revenue Code of 1986, as amended or other applicable tax law. Certain plan participants previously purchased our shares with such promissory notes. The largest aggregate amount outstanding since the first issuance of the promissory notes was US$7.0 million. All amounts outstanding under the promissory notes have been settled.

Repayment of the Promissory Notes. The terms, repayment provisions, and collateral release provisions of the note and the pledge securing the note shall conform with all applicable rules and regulations, including those of the Federal Reserve Board of the United States and any applicable law, as then in effect.

Eligibility. The plan administrators may decide that an award under the 2019 Plan be granted to any employee, officer or director of the Company or its affiliates, or that it be granted to any consultant or advisor who provides services to the Company or its affiliates.

Award Agreements. Each award under the 2019 Plan shall be evidenced by an award agreement in the form approved by the plan administrators. The terms of the award agreements will be determined by the plan administrators and consistent with the terms of the 2019 Plan.

Conditions of Award. The plan administrators shall determine the participants, types of awards, numbers of shares to be covered by awards, terms and conditions of each award, including, but not limited to, the price and number of securities to be offered or awarded, the installments (if applicable) in which such awards will become exercisable or will vest, performance targets (if applicable), the events of termination or reversion of such awards.

Transfer Restrictions. With a few exceptions, no right of interest of a participant in any award may be subject in any manner to sale, transfer, anticipation, alienation, assignment, pledge, encumbrance or charge. This restriction does not apply to (i) transfers to our company, (ii) transfers by gift or domestic relations order to one or more family members, (iii) the designation of a beneficiary to receive benefits if a participant dies or transfers by will, (iv) permitted transfers or exercises on behalf of a participant by the participant's duly authorized legal representative if the participant has suffered a disability.

Reduction or Clawback of Awards. The awards granted under the 2019 Plan are subject to the terms of our recoupment, clawback or similar policy as it may be in effect from time to time, as well as any similar provisions of applicable law, any of which could in certain circumstances require repayment or forfeiture of awards or any ordinary shares or other cash or property received with respect to the awards (including any value received from a disposition of the shares acquired upon payment of the Awards).

Amendment and Termination of the 2019 Plan. The board of directors may, at any time, terminate or, from time to time, amend, modify or suspend the 2019 Plan, in whole or in part. No awards may be granted during any period that the board of directors suspends the 2019 Plan. To the extent then required by applicable law or listing agency, any amendment to the 2019 Plan may be subject to shareholder approval. Unless earlier terminated by the board of directors, the 2019 Plan will terminate at the close of business on the day before the 10th anniversary of the date the board of directors approved the 2019 Plan.

Adagene Inc. 2021 Performance Incentive Plan

In January 2021, our board of directors adopted, and our shareholders approved, the 2021 Performance Incentive Plan, or the 2021 Plan, to provide an additional means through the grant of awards to attract, motivate, retain and reward selected employees and other eligible persons. The terms of the 2021 Plan are summarized below. Employees, officers, directors and consultants that provide services to us or one of our subsidiaries may be selected to receive awards under the 2021 Plan.

Our board of directors or a committee appointed by the board administers the 2021 Plan. The plan administrator has broad authority to:

- select participants and determine the types of awards that they are to receive;
- determine the number of shares that are to be subject to awards and the terms and conditions of awards, including the price (if any) to be paid for the shares or the award and establish the vesting conditions (if applicable) of such shares or awards;
- cancel, modify or waive our rights with respect to, or modify, discontinue, suspend or terminate any or all outstanding awards, subject to any required consents;
- construe and interpret the terms of the 2021 Plan and any agreements relating to the plan;
- accelerate or extend the vesting or exercisability or extend the term of any or all outstanding awards subject to any required consent;
- subject to the other provisions of the 2021 Plan, make certain adjustments to one or more outstanding awards (including a repricing of the exercise or base price of any outstanding option or share appreciation right without shareholder approval) and authorize the termination, conversion, substitution or succession of awards; and
- allow the purchase price of an award or our ordinary shares to be paid in the form of cash, check or electronic funds transfer, by the delivery of previously-owned ordinary shares or by a reduction of the number of shares deliverable pursuant to the award, by services rendered by the recipient of the award, by notice and third party payment or cashless exercise on such terms as the plan administrator may authorize or any other form permitted by law.

A total of 2,994,000 of our ordinary shares was authorized for issuance with respect to awards granted under the 2021 Plan. The share limit will automatically increase on the first trading day in January of each year (commencing with 2022) by an amount equal to (1) 5% of the total number of our outstanding ordinary shares on December 31 of the prior year, or (2) such lesser number as determined by our board of directors. Any shares subject to awards granted under the 2021 Plan or our Second Amended and Restated Share Incentive Plan that are not paid, delivered or exercised before they expire or are canceled or terminated, or otherwise fail to vest, as well as shares used to pay the purchase or exercise price of such awards or related tax withholding obligations, will become available for new award grants under the 2021 Plan. On January 7, 2022, the Company passed a board resolution, pursuant to which the vesting schedules and conditions of 2,060,308 share options granted to certain employees were modified. The share options vested (or to be vested) for each year (commencing from 2021) shall be equal to the lesser of (i) 25% of the total number of share options of each grantee ("Annual Cap") and (ii) the number of shares as determined by the Compensation Committee based on the extent to which any performance milestones were achieved during that year ("Credited Shares"), plus any Credited Share of earlier years that have not previously vested due to the Annual Cap. In addition, the performance milestones applicable to the share options that remain outstanding were also modified. As of March 31, 2023, we had granted equity awards representing 3,979,160 ordinary shares under the 2021 Plan, excluding awards that were forfeited, cancelled or exercised after the relevant grant dates. As of March 31, 2023, 4,324,177 ordinary shares authorized under the 2021 Plan is available for award purposes. Such number includes an annual automatic increase in an amount equal to 5% of the total number of outstanding ordinary shares on December 31, 2022.

Awards under the 2021 Plan may be in the form of incentive or nonqualified stock options, share appreciation rights, share bonuses, restricted shares, share units, restricted share units and other forms of awards including cash awards. Awards under the plan generally will not be transferable other than by will or the laws of descent and distribution, except that the plan administrator may authorize certain transfers.

Options and share appreciation rights may not be granted under the 2021 Plan at exercise prices below the fair market value of the underlying ordinary shares on the date of grant, except that the plan administrator may grant such awards with exercise prices below the fair market value of the underlying shares to service-providers who are not subject to U.S. taxes. The maximum term of options and share appreciation rights granted under the plan is ten years. Incentive stock options granted to any 10% owner of our ordinary shares must have an exercise price that is at least 110% of the fair market value of our ordinary shares on the grant date and a maximum term of five years. These and other awards may also be issued solely or in part for services. Awards are generally paid in cash or our ordinary shares. The plan administrator may provide for the deferred payment of awards and may determine the terms applicable to deferrals.

As is customary in incentive plans of this nature, the number and type of shares available under the 2021 Plan and any outstanding awards, as well as the exercise or purchase prices of awards, will be subject to adjustment in the event of certain reorganizations, mergers, combinations, recapitalizations, share splits, share dividends or other similar events that change the number or kind of shares outstanding, and extraordinary dividends or distributions of property to the shareholders.

Generally, and subject to limited exceptions set forth in the 2021 Plan, if we dissolve or undergo certain corporate transactions such as a merger, business combination or other reorganization, or a sale of all or substantially all of our assets, all awards then-outstanding under the 2021 Plan will become fully vested or paid, as applicable, and will terminate or be terminated in such circumstances, unless the plan administrator provides for the assumption, substitution or other continuation of the award. The plan administrator also has the discretion to establish other change in control provisions with respect to awards granted under the 2021 Plan. For example, the administrator could provide for the acceleration of vesting or payment of an award in connection with a corporate event that is not described above and provide that any such acceleration shall be automatic upon the occurrence of any such event.

Our board of directors may amend or terminate the 2021 Plan at any time, but no such action will affect any outstanding award in any manner materially adverse to a participant without the consent of the participant. Plan amendments will be submitted to shareholders for their approval as required by applicable law or deemed necessary or advisable by the board. The 2021 Plan is not exclusive; our board of directors and compensation committee may grant shares and performance incentives or other compensation, in shares or cash, under other plans or authority.

The plan will terminate on January 16, 2031. However, the plan administrator will retain its authority until all outstanding awards are exercised or terminated.

The following table summarizes, as of March 31, 2023, the number of ordinary shares under outstanding awards that we granted to our directors and executive officers under the 2019 Plan, which replaced the 2015 Plan, and under the 2021 Plan, excluding awards that were exercised, forfeited or canceled after the relevant grant dates.

Name	Ordinary Shares Underlying Equity Awards Granted	Exercise Price (US$/Share)	Date of Grant	Date of Expiration
Executive Officers				
Peter Luo, Ph. D.	287,415	$ 13.85	January 2021	January 2031
Peter Luo, Ph. D.	500,000	$ 5.6	February 2022	February 2032
Peter Luo, Ph. D.	372,819	$ 1.06	December 2022	December 2032
Peter Luo, Ph. D.	202,973	$ 1.06	December 2022	December 2032
Fangyong (Felix) Du, Ph. D.	111,744	$ 13.85	January 2021	January 2031
Fangyong (Felix) Du, Ph. D.	150,000	$ 5.6	February 2022	February 2032
Fangyong (Felix) Du, Ph. D.	152,452	$ 1.06	December 2022	December 2032
JC Xu, M.D., Ph. D.	*	$ 2.26	August 2020	August 2030
JC Xu, M.D., Ph. D.	*	$ 1.06	December 2022	December 2032
Qinghai Zhao, Ph. D.	*	$ 2.26	October 2020	October 2030
Qinghai Zhao, Ph. D.	*	$ 5.6	February 2022	February 2032
Qinghai Zhao, Ph. D.	*	$ 1.06	December 2022	December 2032
Man Kin (Raymond) Tam, M.B.A., B. Eng.	*	$ 1.48	March 2020	March 2030
Man Kin (Raymond) Tam, M.B.A., B. Eng.	*	$ 1.83	August 2020	August 2030
Man Kin (Raymond) Tam, M.B.A., B. Eng.	*	$ 1.06	December 2022	December 2032
Chunfang (Vicky) Gu	*	$ 1.33	February 2019	February 2029
Chunfang (Vicky) Gu	*	$ 1.48	March 2020	March 2030
Chunfang (Vicky) Gu	*	$ 1.83	August 2020	August 2030
Chunfang (Vicky) Gu	*	$ 5.6	February 2022	February 2032
Chunfang (Vicky) Gu	*	$ 1.06	December 2022	December 2032
Ling (Jolin) Zhou	*	$ 1.48	March 2020	March 2030
Ling (Jolin) Zhou	*	$ 1.83	August 2020	August 2030
Ling (Jolin) Zhou	*	$ 5.6	February 2022	February 2032
Ling (Jolin) Zhou	*	$ 1.06	December 2022	December 2032
Non-Employee Directors				
Yumeng Wang	—	—	—	—
Andy (Yiu Leung) Cheung	*	$ 11.2	June 2021	June 2031
Min Li	*	$ 11.2	June 2021	June 2031
Yuwen Liu	*	$ 2.24	May 2022	May 2032
Cuong Do	*	$ 0.8	November 2022	November 2032
Mervyn Turner	*	$ 1.33	November 2018	November 2028
All directors and executive officers as a group	3,508,641		Various dates from November 2018 to December 2022	Various dates from November 2028 to December 2032

Note:
* The shares held by each of these directors and executive officers represent less than 1% of our total outstanding shares.

As of March 31, 2023, our award holders other than our directors and executive officers as a group held outstanding awards to purchase 3,185,333 ordinary shares. For discussions of our accounting policies and estimates for awards granted pursuant to the 2019 Plan and 2021 Plan, see "Item 5 Operating and Financial Review and Prospects—Share-based compensation."

6.C. Board Practices

Board of Directors

Our board of directors currently consists of nine directors, including five independent directors, namely Andy (Yiu Leung) Cheung, Min Li, Yuwen Liu, Cuong Do and Mervyn Turner. Yuwen Liu will depart from our board and applicable committee upon the filing of this annual report on Form 20-F. A director is not required to hold any shares in our company to qualify to serve as a director. The Corporate Governance Rules of the Nasdaq generally require that a majority of an issuer's board of directors must consist of independent directors. However, the Corporate Governance Rules of the Nasdaq permit foreign private issuers like us to follow "home country practice" in certain corporate governance matters. We rely on this "home country practice" exception and do not have a majority of independent directors serving on our board of directors , our compensation committee and our nominating and corporate governance committee.

A director who is in any way, whether directly or indirectly, interested in a contract or proposed contract with our company is required to declare the nature of his or her interest at a meeting of our directors. A general notice given to the directors by any director to the effect that he or she is a member, shareholder, director, partner, officer or employee of any specified company or firm and is to be regarded as interested in any contract or transaction with that company or firm shall be deemed a sufficient declaration of interest for the purposes of voting on a resolution in respect to a contract or transaction in which he/she has an interest, and after such general notice it shall not be necessary to give special notice relating to any particular transaction. Subject to our memorandum and articles of association, as amended n restated from time to time, our company may by ordinary resolution appoint any person to be a director and the board may, by affirmative vote of a simple majority of the remaining directors present and voting at a board meeting, appoint any person as a director to fill a casual vacancy or as an addition to the existing board. A director may vote in respect of any contract or proposed contract or arrangement notwithstanding that he/she may be interested therein and if he/ she does so, his/her vote shall be counted and he/she may be counted in the quorum at any meeting of the directors at which any such contract or proposed contract or arrangement is considered, subject to any separate requirement for Audit Committee approval under applicable law or the Listing Rules of the Nasdaq. Our board of directors may exercise all of the powers of our company to borrow money, to mortgage or charge its undertaking, property and uncalled capital, or any part thereof, and to issue debentures, debenture stock or other securities whenever money is borrowed or as security for any debt, liability or obligation of our company or of any third party. None of our directors has a service contract with us that provides for benefits upon termination of service as a director.

Committees of the Board of Directors

We have established an audit committee, a compensation committee and a nominating and corporate governance committee under our board of directors. We have also adopted a charter for each of the three committees. Each committee's members and functions are described below.

Audit Committee. Our audit committee consists of Andy (Yiu Leung) Cheung, Min Li, Yuwen Liu and Cuong Do, and is chaired by Andy (Yiu Leung) Cheung. We have determined that each of Andy (Yiu Leung) Cheung, Min Li, Yuwen Liu and Cuong Do satisfies the requirements of Rule 5605(a)(2) of the Listing Rules of the Nasdaq and meets the independence standards under Rule 10A-3 under the Securities Exchange Act of 1934, as amended. Yuwen Liu will depart from our board and audit committee upon the filing of this annual report on Form 20-F. We have determined that Andy (Yiu Leung) Cheung qualifies as an "audit committee financial expert." The audit committee oversees our accounting and financial reporting processes and the audits of the financial statements of our company. The audit committee is responsible for, among other things:

- reviewing and recommending to our board for approval, the appointment, re-appointment or removal of the independent auditor, after considering its annual performance evaluation of the independent auditor;
- approving the remuneration and terms of engagement of the independent auditor and pre-approving all auditing and non-auditing services permitted to be performed by our independent auditors at least annually;

- obtaining a written report from our independent auditor describing matters relating to its independence and quality control procedures;
- reviewing with the independent registered public accounting firm any audit problems or difficulties and management's response;
- discussing with our independent auditor, among other things, the audits of the financial statements, including whether any material information should be disclosed, issues regarding accounting and auditing principles and practices;
- reviewing and approving all proposed related party transactions, as defined in Item 404 of Regulation S-K under the Securities Act;
- reviewing and recommending the semi-annually financial data the annual financial statements to our board for inclusion in our semi-annually earnings releases and annual reports, respectively;
- discussing the annual audited financial statements with management and the independent registered public accounting firm;
- reviewing the adequacy and effectiveness of our accounting and internal control policies and procedures and any special steps taken to monitor and control major financial risk exposures;
- at least annually, reviewing and reassessing the adequacy of the committee charter;
- approving annual audit plans, and undertaking an annual performance evaluation of the internal audit function;
- establishing and overseeing procedures for the handling of complaints and whistleblowing;
- meeting separately and periodically with management and the independent registered public accounting firm;
- monitoring compliance with our code of business conduct and ethics, including reviewing the adequacy and effectiveness of our procedures to ensure proper compliance; and
- reporting regularly to the board.

Compensation Committee. Our compensation committee consists of Peter Luo, Andy (Yiu Leung) Cheung and Min Li and is chaired by Peter Luo. We have determined that each of Andy (Yiu Leung) Cheung and Min Li satisfies the "independence" requirements of Rule 5605(a)(2) of the Listing Rules of the Nasdaq. The compensation committee assists the board in reviewing and approving the compensation structure, including all forms of compensation, relating to our directors and executive officers. Our Chief Executive Officer may not be present at any committee meeting during which their compensation is deliberated upon. The compensation committee is responsible for, among other things:

- overseeing the development and implementation of compensation programs in consultation with our management;
- at least annually, reviewing and approving, or recommending to the board for its approval, the compensation for our executive officers;
- at least annually, reviewing and recommending to the board for determination with respect to the compensation of our non-executive directors;
- at least annually, reviewing periodically and approving any incentive compensation or equity plans, programs or other similar arrangements;
- reviewing executive officer and director indemnification and insurance matters;

- overseeing our regulatory compliance with respect to compensation matters, including our policies on restrictions on compensation plans and loans to directors and executive officers;
- at least annually, reviewing and reassessing the adequacy of the committee charter;
- selecting compensation consultant, legal counsel or other advisor only after taking into consideration all factors relevant to that person's independence from management; and
- reporting regularly to the board.

Nominating and Corporate Governance Committee. Our nominating and corporate governance committee consists of Peter Luo, Andy (Yiu Leung) Cheung and Min Li, and is chaired by Peter Luo. We have determined that each of Andy (Yiu Leung) Cheung and Min Li satisfies the "independence" requirements of Rule 5605(a)(2) of the Listing Rules of the Nasdaq. The nominating and corporate governance committee assists the board in selecting individuals qualified to become our directors and in determining the composition of the board and its committees. The nominating and corporate governance committee is responsible for, among other things:

- recommending nominees to the board for election or re-election to the board, or for appointment to fill any vacancy on the board;
- reviewing annually with the board the current composition of the board with regards to characteristics such as independence, knowledge, skills, experience, expertise, diversity and availability of service to us;
- developing and recommending to our board such policies and procedures with respect to nomination or appointment of members of our board and chairs and members of its committees or other corporate governance matters as may be required pursuant to any SEC or Nasdaq rules, or otherwise considered desirable and appropriate;
- selecting and recommending to the board the names of directors to serve as members of the audit committee and the compensation committee, as well as of the nominating and corporate governance committee itself;
- at least annually, reviewing and reassessing the adequacy of the committee charter;
- developing and reviewing at least annually the corporate governance principles adopted by the board and advising the board with respect to significant developments in the law and practice of corporate governance and our compliance with such laws and practices; and
- evaluating the performance and effectiveness of the board as a whole.

Duties and Functions of Directors

Under Cayman Islands law, our directors owe fiduciary duties to our company, including a duty of loyalty, a duty to act honestly and a duty to act in what they consider in good faith to be in our best interests. Our directors must also exercise their powers only for a proper purpose. Our directors also owe to our company a duty to exercise the skill they actually possess and such care and diligence that a reasonable prudent person would exercise in comparable circumstances. It was previously considered that a director need not exhibit in the performance of his duties a greater degree of skill than may reasonably be expected from a person of his knowledge and experience. However, English and Commonwealth courts have moved towards an objective standard with regard to the required skill and care and these authorities are likely to be followed in the Cayman Islands. In fulfilling their duty of care to us, our directors must ensure compliance with our memorandum and articles of association, as amended and restated from time to time. Our company has the right to seek damages if a duty owed by our directors is breached. In limited exceptional circumstances, a shareholder may have the right to seek damages in our name if a duty owed by our directors is breached. The functions and powers of our board of directors include, among others, (i) convening shareholders' annual general meetings and reporting its work to shareholders at such meetings, (ii) declaring dividends, (iii) appointing officers and determining their terms of offices and responsibilities, (iv) exercising the borrowing powers of our company, and (v) approving the transfer of shares of our company, including the registering of such shares in our share register.

Terms of Directors and Officers

Our officers are elected by and serve at the discretion of the board of directors. Other than Andy (Yiu Leung) Cheung, Min Li, Yuwen Liu, Man Kin (Raymond) Tam, Felix Du, Cuong Do and Mervyn Turner, each director is not subject to a term of office and holds office until such time as his successor takes office or until the earlier of his death, resignation or removal from office pursuant to the applicable provisions of our memorandum and articles of association. The current term of our independent directors, namely Andy (Yiu Leung) Cheung, Min Li and Mervyn Turner, is one-year from the date of filing of this annual report on Form 20-F. The initial term of our independent director Cuong Do is two-year from the effectiveness of the appointment. Each of Andy (Yiu Leung) Cheung, Min Li and Yuwen Liu's initial term has been extended to April 2023 and will expire upon the filing of this annual report on Form 20-F. The Board has decided to renew Andy (Yiu Leung) Cheung, Min Li and Man Kin (Raymond) Tam's term of director position for one year. The term of director position for each of Andy (Yiu Leung) Cheung, Man Kin (Raymond) Tam, Felix Du, Min Li, Cuong Do and Mervyn Turner is subject to re-appointment by the board of directors. A director will be removed from office automatically if, among other things, the director (i) becomes bankrupt or makes any arrangement or composition with his creditors; (ii) dies or is found by our company to be of unsound mind; (iii) resigns by notice in writing to our company; (iv) without special leave of absence from our board of directors, is absent from three consecutive meetings of the board and the board resolves that his office be vacated; (v) is prohibited by law or the Listing Rules of the Nasdaq Global Market from being a director; or (vi) is removed from office pursuant to any other provisions of our post-offering amended and restated memorandum and articles of association.

Board Diversity

The board diversity matrix is set out below.

Board Diversity Matrix (As of the Date of This Annual Report)

Country of Principal Executive Offices	The People's Republic of China			
Foreign Private Issuer	Yes			
Disclosure Prohibited under Home Country Law	No			
	Female	**Male**	**Non-Binary**	**Did Not Disclose Gender**
Part I: Gender Identity				
Directors	2*	7	0	0
Part II: Demographic Background				
Underrepresented Individual in Home Country Jurisdiction			—	
LGBTQ+			—	
Did Not Disclose Demographic Background			—	

Note: *Yumen Liu, a female director, will depart from our board upon filing of this annual report.

Interested Transactions

A director may, subject to any separate requirement for audit and risk committee approval under applicable law or applicable Nasdaq listing rules, vote in respect of any contract or transaction in which he or she is interested, provided that the nature of the interest of any directors in such contract or transaction is disclosed by him or her at or prior to its consideration and any vote in that matter.

6.D. Employees

We had a total of 198, 259 and 248 employees as of December 31, 2020, 2021 and 2022, respectively. The following table sets forth the numbers of our employees categorized by function as of December 31, 2022. We also engage consultants and part-time staff as and when appropriate.

Function	Number of Employees	
Research and Development		196
Computational Biology and Informatics	32	
Technology Development	67	
Drug Discovery	50	
Clinical Development	36	
CMC Development	11	
General Administration		49
HR	6	
Finance	18	
IT	12	
Administration	13	
Business Development and Marketing		3
Total		248

Our success depends on our ability to attract, motivate, train and retain qualified personnel. We believe we offer our employees competitive compensation packages and an environment that encourages self-development. We regularly recruit new talents through campus events and colleague referral to build and develop our own talent pool. Through employee succession planning, we help employees understand their career path within Adagene, motivate them to remain in the organization and to achieve their personal career goals. Other initiatives for talent retention include executive coaching, employee surveys or engagement, training and development, compensation and rewards. As a result of these efforts, we have generally been able to attract and retain qualified personnel and maintain a stable core management team.

As required by regulations in China, we participate in various employee social security plans that are organized by municipal and provincial governments, including pension insurance, unemployment insurance, maternity insurance, work-related injury insurance, medical insurance and housing funds. We are required under PRC law to make contributions to employee benefit plans at specified percentages of the salaries, bonuses and certain allowances of our employees, up to a maximum amount specified by the local government from time to time. We have granted, and plan to continue to grant, share-based incentive awards to our employees in the future to incentivize their contributions to our growth and development.

We believe that we maintain a good working relationship with our employees, and we have not experienced any material labor disputes. None of our employees is requested by labor unions.

6.E. Share Ownership

The following table sets forth information concerning the beneficial ownership of our ordinary shares, as of March 31, 2023, by:

- each of our directors and executive officers; and

- each person known to us to beneficially own more than 5% of our ordinary shares.

The calculations in the table below are based on 54,715,839 ordinary shares issued and outstanding as of March 31, 2023, excluding the 832,500 ordinary shares, issued but deemed to be not outstanding as of March 31, 2023, held by Great Han Fortune LP.

Beneficial ownership is determined in accordance with the rules and regulations of the SEC. In computing the number of shares beneficially owned by a person and the percentage ownership of that person, we have included shares that the person has the right to acquire within 60 days, including through the exercise of any option, warrant, or other right or the conversion of any other security.

These shares, however, are not included in the computation of the percentage ownership of any other person.

	Ordinary Shares Beneficially Owned as of March 31, 2023	
	Number	%*
Directors and Executive Officers:†		
Peter Luo(1)	12,799,269	23.4 %
Fangyong (Felix) Du(2)	1,303,938	2.4 %
JC Xu	**	** %
Qinghai Zhao	**	** %
Man Kin (Raymond) Tam	**	** %
Chunfang (Vicky) Gu	**	** %
Ling (Jolin) Zhou	**	** %
Non-employee Directors		
Yumeng Wang	—	— %
Andy (Yiu Leung) Cheung (independent director)	**	** %
Min Li (independent director)	**	** %
Yuwen Liu (independent director)	**	** %
Cuong Do (independent director)	**	** %
Mervyn Turner (independent director)	**	** %
All directors and executive officers as a group	**13,014,227**	**23.8 %**
Principal Shareholders:		
Peter Luo act-in-concert group(3)	12,799,269	23.4 %
JSR Limited(4)	5,340,742	9.8 %
Asia Ventures II L.P.(5)	4,826,037	8.8 %
F-Prime Capital Partners Healthcare Fund III LP(6)	4,632,237	8.5 %
Wuxi Pharmatech Healthcare Fund I L.P.(7)	5,282,120	9.7 %
General Atlantic Singapore AI Pte. Ltd.(8)	4,782,441	8.7 %

Notes:

* For each person and group included in this table, percentage ownership is calculated by dividing the number of shares beneficially owned by such person or group by the sum of (i) 54,715,839 being the number of ordinary shares as of March 31, 2023 and (ii) the number of ordinary shares underlying share options held by such person or group that are exercisable within 60 days after March 31, 2023.

** Represents beneficial ownership of less than one percent.

† The business address of our directors and executive officers, except for Cuong Do, Yumeng Wang, Yuwen Liu and Mervyn Turner, is 4F, Building C14, No. 218, Xinghu Street, Suzhou Industrial Park Suzhou, Jiangsu Province, 215123, People's Republic of China. The business address of Yumeng Wang is Suite 5704-5706, 57F, Two IFC, 8 Finance Street, Central, Hong Kong; the business address of Yuwen Liu is 3 Fl, Building No. 10, Dongshahu Equity Investment Center, East Suhong Road, Suzhou Industrial Park; the business address of Cuong Do is 660 Destacada Ave, Miami, United States FL 33156-8000; and the business address of Mervyn Turner is MJ Turner Consulting LLC, Westfield, NJ, USA.

(1) Represents 12,799,269 ordinary shares held by Peter Luo act-in-concert group, as set forth in note (3) below.

(2) Represents (i) 785,944 ordinary shares held by Ping Ren, who is the spouse of Fangyong (Felix) Du, (ii) 397,500 ordinary shares held by Great Han Fortune LP for the benefit of Ping Ren, (iii) 5,000 ordinary shares held by Great Han Fortune LP for the benefit of Ping Ren that are vested or will be vested within 60 days of March 31, 2023, (iv) 115,494 ordinary shares underlying 115,494 share options granted to Ping Ren that that are vested or will be vested within 60 days of March 31, 2023. Great Han Fortune LP is controlled by Peter Luo and is formed to hold ordinary shares in connection with the share awards issued under the 2019 Plan.

(3) Represents (i) 8,035,316 ordinary shares held by Peter Luo; (ii) 337,415 ordinary shares underlying share options granted to Peter Luo that are vested or will be vested within 60 days of March 31, 2023, (iii) 766,667 ordinary shares held by Great Han Fortune LP for the benefit of Peter Luo and (iv) 33,333 ordinary shares held by Great Han Fortune LP for the benefit of Peter Luo that will be vested within 60 days of March 31, 2023; (v) 0 ordinary shares held by HAN 2020 GRAT, for which Peter Luo is a Trustee; (vi) 52,198 ordinary shares held by Xiaohong She, who is the spouse of Peter Luo; (vii) 48,230 ordinary shares underlying share options granted to Xiaohong She that are vested or will be vested within 60 days of March 31, 2023, (viii) 192,083 ordinary shares held by Great Han Fortune LP for the benefit of Xiaohong She, (ix) 4,167 ordinary shares held by Great Han Fortune LP for the benefit of Xiaohong She that will be vested within 60 days of March 31, 2023; (x) 785,944 ordinary shares held by Ping Ren, who is the spouse of Fangyong (Felix) Du, (xi) 397,500 ordinary shares held by Great Han Fortune LP for the benefit of Ping Ren, (xii) 5,000 ordinary shares held by Great Han Fortune LP for the benefit of Ping Ren that are vested or will be vested within 60 days of March 31, 2023, (xiii) 115,494 ordinary shares underlying 115,494 share options granted to Ping Ren that that are vested or will be vested within 60 days of March 31, 2023, (xiv) total of 1,312,357 ordinary shares held by Raymond Tam, JC Xu, Qinghai Zhao and several key employees of the Company, and (xv) total of 713,565 share options granted to Raymond Tam, JC Xu, Qinghai Zhao and several key employees that are vested or will be vested within 60 days of March 31, 2023. On December 14, 2020, Peter Luo, Fangyong (Felix) Du, Ping Ren, Hua Gong, JC Xu, Qinghai Zhao, Man Kin (Raymond) Tam, Xiaohong (Kristine) She, Yu (Albert) Ren, Yan Li, Guizhong Liu and Alexander Goergen entered into a concert party agreement, pursuant to which the parties agree to (i) always be acting in concert in respect of their respective direct or indirect voting rights at our shareholders' general meetings, (ii) recognize the controlling position of Peter Luo; and (iii) act in concert in accordance with Peter Luo's opinions in respect of the daily operations and management and the major decision-making of us.

(4) Represents 5,340,742 ordinary shares, consisting of (i) 4,828,242 ordinary shares and (ii) 512,500 ordinary shares in the form of ADSs, are held of record by JSR Limited, a British Virgin Islands company. JSR Limited is controlled by GP Healthcare Capital Co., Ltd. The registered address of JSR Limited is Vistra Corporate Services Centre, Wickhams Cay II, Road Town, Tortola, VG1110, British Virgin Islands. Information set forth above is based upon JSR Limited's Schedule 13G/A filing with the SEC on February 6, 2023.

(5) Represents 4,826,037 ordinary shares held by Asia Ventures II L.P., a limited partnership incorporated in the Bermuda. The general partner of Asia Ventures II L.P. is Asia Partners II L.P. a Bermuda exempt limited partnership. The general partner of Asia Partners II L.P. is Eight Roads GP, who is ultimately controlled by Eight Roads Holdings Limited. The registered address of Asia Ventures II L.P. is Pembroke Hall, 42 Crow Lane, Pembroke, Bermuda HM 19. Information set forth above is based upon FIL Ltd's Schedule 13G filing with the SEC on February 19, 2021.

(6) Represents 4,632,237 ordinary shares held by F-Prime Capital Partners Healthcare Fund III LP. F-Prime Capital Partners Healthcare Advisors Fund III LP is the general partner of F-Prime Capital Partners Healthcare Fund III LP. F-Prime Capital Partners Healthcare Advisors Fund III LP is solely managed by Impresa Management LLC, its general partner and investment manager. Each of the entities listed above expressly disclaims beneficial ownership of the securities listed above except to the extent of any pecuniary interest therein. The address of these entities is 245 Summer Street, Boston, MA 02210. Information set forth above is based upon FMR LLC's Schedule 13G/A filing with the SEC on February 9, 2023.

(7) Represents 5,282,120 ordinary shares in the form of ADSs that were held of record by WuXi PharmaTech Healthcare Fund I L.P., a limited partnership incorporated in the Cayman Islands. WuXi Pharmatech Healthcare Fund I L.P. is an indirect wholly owned subsidiary of WuXi AppTec Co., Ltd (SSE: 603259; SEHK: 2359). WuXi AppTec Co., Ltd. is a listed company on the Shanghai Stock Exchange and the Main Board of the Hong Kong Stock Exchange. The registered address of WuXi Pharmatech Healthcare Fund I L.P. is P.O. Box 309, Ugland House, Grand Cayman, KY1-1104, Cayman Islands. Information set forth above is based upon WuXi PharmaTech Healthcare Fund I L.P's Schedule 13G filing with the SEC on January 26, 2022.

(8) Represents 4,452,441 ordinary shares and 264,000 ADSs representing 330,000 ordinary shares held by General Atlantic Singapore AI Pte. Ltd. (“GA AI”), a company incorporated under the laws of Singapore. GA AI is wholly-owned by General Atlantic Singapore Fund Pte. Ltd. (“GASF”), which is controlled by General Atlantic Singapore Interholdco Ltd. (“GAS Interholdco”) The members of GAS Interholdco that share beneficial ownership of the ordinary shares and ADSs held of record by GA AI are the GA Funds. The general partner of General Atlantic Partners (Lux) SCSp (“GAP Lux”) is General Atlantic GenPar, (Lux) SCSp (“GA GenPar Lux”) and the general partner of GA GenPar Lux is General Atlantic (Lux) S.à. r.l. (“GA Lux”). The general partner of General Atlantic Partners (Bermuda) EU, L.P. (“GAP Bermuda EU”) and General Atlantic Partners (Bermuda) IV, L.P. (“GAP Bermuda IV”) and the sole shareholder of GA Lux is General Atlantic GenPar (Bermuda), L.P. (“GenPar Bermuda”). GAP (Bermuda) L.P., which is controlled by the Management Committee of GASC MGP, LLC (the “GA Management Committee”), is the general partner of GenPar Bermuda. General Atlantic, L.P. (“GA LP”), which is also controlled by the GA Management Committee, is the managing member of GAP Coinvestments III, LLC (“GAPCO III”), GAP Coinvestments IV, LLC (“GAPCO IV”) and GAP Coinvestments V, LLC (“GAPCO V”) and the general partner of GAP Coinvestments CDA, L.P. (“GAPCO CDA”). GAP Bermuda IV, GAP Bermuda EU, GAP Lux, GAPCO III, GAPCO IV, GAPCO V and GAPCO CDA are collectively referred to as the “GA Funds.” There are nine members of the GA Management Committee as of the date hereof. Each of the members of the GA Management Committee disclaims ownership of the ordinary shares, the ADSs and the underlying ordinary shares except to the extent that he has a pecuniary interest therein. The registered address of General Atlantic Singapore AI Pte. Ltd. is 80 Robinson Road, #02-00 Singapore 068898. Information set forth above is based upon General Atlantic, L.P.’s Schedule 13G filing with the SEC on February 11, 2022.

As of March 31, 2023, a total of 25,831,040 ordinary shares, representing 47.2% of our outstanding ordinary shares, including ordinary shares issued in advance but deemed not outstanding to facilitiate conversation of ordinary shares to ADSs for the employee share incentive plans, are held by one record holder in the United States. The holder is the depositary of our ADS program. In addition, 26.0% of our outstanding ordinary shares were held by record holders in the United States.

Our principal shareholders do not have different voting rights. We are not aware of any arrangement that may, at a subsequent date, result in a change of control of our company.

6.F. Disclosure of a Registrant's Action to Recover Erroneously Awarded Compensation.

None.

Item 7. Major Shareholders and Related Party Transactions

7.A. Major Shareholders

Please refer to “Item 6. Directors, Senior Management and Employees — E. Share Ownership.”

7.B. Related Party Transactions

The following is a summary of transactions since January 1, 2022 to which we have been a participant in which any of our then directors, executive officers or holders of more than 10% of any class of our voting securities at the time of such transaction, or any members of their immediate family, had or will have a direct or indirect material interest.

Employment Agreements and Indemnification Agreements

See “Item 6 Directors, Senior Management and Employees—6.B. Compensation—Employment Agreements and Indemnification Agreements.”

Share Incentives

See “Item 6 Directors, Senior Management and Employees—6.B. Compensation—Share Incentive Plan.”

Other Related Party Transactions

Transactions with WuXi AppTec Group

We received research and development services from WuXi AppTec Group, the parent company of one of our principal shareholders. The amounts for the purchase of the services were US$7.4 million in 2022. As of December 31, 2022, the amounts due to WuXi AppTec Group were US$1.5 million.

Transactions with WuXi Biologics (Cayman) Inc. or WuXi Biologics

We received research and development services, including provision of manufacturing and quality control testing services, from WuXi Biologics, an entity controlled by the ultimate controlling party of one of our principal shareholders. The amounts for the purchase of the services were US$27.8 million in 2022. As of December 31, 2022, the amounts due to WuXi Biologics were US$17.8 million.

7.C. Interests of Experts and Counsel

Not applicable.

Item 8. Financial Information

8.A. Consolidated Statements and Other Financial Information

We have appended consolidated financial statements filed as part of this annual report.

Legal and Administrative Proceedings

As of the date of this annual report, we are not a party to any material legal or administrative proceedings. We may from time to time be subject to various legal or administrative claims and proceedings arising in the ordinary course of business. Litigation or any other legal or administrative proceeding, regardless of the outcome, is likely to result in a substantial cost and diversion to our resources, including our management's time and attention. For risks relating to legal and administrative proceedings against us, please see "Item 3 Key Information—D. Risk Factors—Risks Relating to Our Operations—Allegations or lawsuits against us or our management may harm our reputation and business."

Dividend Policy

We have not previously declared or paid cash dividends and we have no plan to declare or pay any dividends in the near future on our shares or the ADSs representing our ordinary shares. We currently intend to retain most, if not all, of our available funds and any future earnings to operate and expand our business.

We are a holding company incorporated in the Cayman Islands. In the future, we may rely on dividends from our subsidiaries, including our PRC and U.S. subsidiaries, for our cash requirements, including any payment of dividends to our shareholders. PRC regulations may restrict the ability of our PRC subsidiary to pay dividends to us. See "Item 4 Information of the Company—B. Business Overview—Regulation—Regulations relating to Dividend Distribution."

Our board of directors has discretion as to whether to distribute dividends, subject to certain requirements of Cayman Islands law. In addition, our shareholders may, subject to the provisions of our post-offering articles of association, by ordinary resolution declare a dividend, but no dividend may exceed the amount recommended by our board of directors. Under Cayman Islands law, a Cayman Islands company may pay a dividend out of either profit, retained earnings or share premium account, provided that in no circumstances may a dividend be paid if this would result in the company being unable to pay its debts as they fall due in the ordinary course of business. Even if our board of directors decides to pay dividends, the form, frequency and amount will depend upon our future operations and earnings, capital requirements and surplus, general financial condition, contractual restrictions and other factors that the board of directors may deem relevant. If we pay any dividends on our ordinary shares, we will pay those dividends which are payable in respect of the ordinary shares underlying the ADSs to the depositary, as the registered holder of such ordinary shares, and the depositary then will pay such amounts to the ADS holders in proportion to the ordinary shares underlying the ADSs held by such ADS holders, subject to the terms of the deposit agreement, including the fees and expenses payable thereunder. See “Item 12 Description of Securities Other Than Equity Securities—D. American Depositary Shares.”

8.B. Significant Changes

Except as otherwise disclosed in this report, we have not experienced any significant changes since the date of the annual financial statements included herein.

Item 9. The Offer and Listing

9.A. Offering and Listing Details

Our ADSs have been listed on the Nasdaq Global Market since February 9, 2021 under the symbol “ADAG.” Each ADS represents one and one quarter ordinary shares, par value US$0.0001 per share.

9.B. Plan of Distribution

Not applicable.

9.C. Markets

Our ADSs have been listed on the Nasdaq Global Market since February 9, 2021 under the symbol “ADAG.”

9.D. Selling Shareholders

Not applicable.

9.E. Dilution

Not applicable.

9.F. Expenses of the Issue

Not applicable.

Item 10. Additional Information

10.A. Share Capital

Not applicable.

10.B. Memorandum and Articles of Association

We are a Cayman Islands exempted company and our affairs are governed by our memorandum and articles of association, as amended and restated from time to time, and Companies Act of the Cayman Islands, and the common law of the Cayman Islands.

We incorporate by reference into this annual report our amended and restated memorandum and articles of association, the form of which was filed as Exhibit 3.2 to our registration statement on Form F-1 (File Number 333-252210), as amended, filed with the Securities and Exchange Commission on February 1, 2021. Our members adopted our amended and restated memorandum and articles of association by a special resolution on January 19, 2021, which became effective immediately prior to completion of our initial public offering of ADSs representing our ordinary shares.

The following are summaries of material provisions of our Seventh Amended and Restated Memorandum and Articles of Association and the Companies Act insofar as they relate to the material terms of our ordinary shares.

Registered Office and Objects

Our registered office in the Cayman Islands is at the offices of Vistra (Cayman) Limited, P. O. Box 31119 Grand Pavilion, Hibiscus Way, 802 West Bay Road, Grand Cayman, KY1 - 1205 Cayman Islands or at such other location as the Directors may from time to time determine.

According to Clause 3 of our Seventh Amended and Restated Memorandum of Association, the objects for which the Company is established are unrestricted and the Company shall have full power and authority to carry out any object not prohibited by any law as provided by Section 7(4) of the Companies Act (as amended) of the Cayman Islands.

Board of Directors

See “Item 6 Directors, Senior Management and Employees.”

Ordinary shares

General. Our authorized share capital is US$80,000 divided into 800,000,000 shares comprising (i) 640,000,000 ordinary shares of a par value of US$0.0001 each, and (ii) 160,000,000 shares of a par value of US$0.0001 each of such class or classes (however designated) as our board of directors may determine in accordance with our amended and restated memorandum and articles of association. Holders of ordinary shares have the same rights. All of our issued and outstanding ordinary shares are fully paid and non-assessable. Certificates representing the ordinary shares are issued in registered form. We may not issue share to bearer. Our shareholders who are nonresidents of the Cayman Islands may freely hold, transfer and vote their ordinary shares.

Dividends. The holders of our ordinary shares are entitled to such dividends as may be declared by our board of directors subject to our post-offering memorandum and articles of association and the Companies Act. In addition, our shareholders may, subject to the provisions of our articles of association, by ordinary resolution declare a dividend, but no dividend may exceed the amount recommended by our directors. Our post-offering memorandum and articles of association provide that dividends may be declared and paid out of our profits, realized or unrealized, or from any reserve set aside from profits which our board of directors determine is no longer needed. Dividends may also be declared and paid out of the share premium account or any other fund or account which can be authorized for this purpose in accordance with the Companies Act. No dividend may be declared and paid unless our directors determine that, immediately after the payment, we will be able to pay our debts as they become due in the ordinary course of business and we have funds lawfully available for such purpose.

Voting Rights. In respect of all matters subject to a shareholders’ vote, holder of an Ordinary Share is entitled to one vote for each Ordinary Share registered in his or her name on our register of members. Voting at any meeting of shareholders is by way of a poll unless a show of hands is permitted. A poll may be demanded by the chairman of such meeting or any one shareholder.

A quorum required for a meeting of shareholders consists of two or more shareholders holding not less than one-half of the votes attaching to the issued and outstanding shares entitled to vote at general meetings present in person or by proxy or, if a corporation or other non-natural person, by its duly authorized representative. As a Cayman Islands exempted company, we are not obliged by the Companies Act to call shareholders' annual general meetings. Our post-offering memorandum and articles of association provide that we may (but are not obliged to) in each year hold a general meeting as our annual general meeting in which case we will specify the meeting as such in the notices calling it, and the annual general meeting will be held at such time and place as may be determined by our board of directors. We, however, will hold an annual shareholders' meeting during each fiscal year, as required by the Listing Rules of the Nasdaq Global Market. Each general meeting, other than an annual general meeting, shall be an extraordinary general meeting. Shareholders' annual general meetings and any other general meetings of our shareholders may be called by a majority of our board of directors or our chairman or upon a requisition of shareholders holding at the date of deposit of the requisition not less than 20% of the votes attaching to the issued and outstanding shares entitled to vote at general meetings, in which case the directors are obliged to call such meeting and to put the resolutions so requisitioned to a vote at such meeting; however, our post-offering memorandum and articles of association do not provide our shareholders with any right to put any proposals before annual general meetings or extraordinary general meetings not called by such shareholders. Advance notice of at least seven (7) days is required for the convening of our annual general meeting and other general meetings in accordance with our post-offering memorandum and articles of association.

An ordinary resolution to be passed at a meeting by the shareholders requires the affirmative vote of a simple majority of the votes attaching to the ordinary shares cast by those shareholders entitled to vote who are present in person or by proxy at a general meeting, while a special resolution also requires the affirmative vote of no less than two-thirds of the votes attaching to the ordinary shares cast by those shareholders entitled to vote who are present in person or by proxy at a general meeting. A special resolution will be required for important matters such as a change of name or making changes to our post-offering memorandum and articles of association.

Transfer of Ordinary Shares. Subject to the restrictions in our post-offering memorandum and articles of association as set out below, any of our shareholders may transfer all or any of his or her ordinary shares by an instrument of transfer in the usual or common form or any other form approved by our board of directors.

Our board of directors may, in its absolute discretion, decline to register any transfer of any Ordinary Share. Our board of directors may also decline to register any transfer of any Ordinary Share unless:

- the instrument of transfer is lodged with us, accompanied by the certificate for the ordinary shares to which it relates and such other evidence as our board of directors may reasonably require to show the right of the transferor to make the transfer;
- the instrument of transfer is in respect of only one class of shares;
- the instrument of transfer is properly stamped, if required;
- in the case of a transfer to joint holders, the number of joint holders to whom the Ordinary Share is to be transferred does not exceed four;
- the shares are free from any lien in favor of us; and
- a fee of such maximum sum as the Nasdaq may determine to be payable or such lesser sum as our directors may from time to time require is paid to us in respect thereof.

If our directors refuse to register a transfer, they shall, within three months after the date on which the instrument of transfer was lodged, send to each of the transferor and the transferee notice of such refusal.

The registration of transfers may, after compliance with any notice requirement of the Nasdaq, be suspended and the register closed at such times and for such periods as our board of directors may from time to time determine, *provided*, *however*, that the registration of transfers shall not be suspended nor the register closed for more than 30 days in any year as our board may determine.

Liquidation. On a return of capital on winding up or otherwise (other than on conversion, redemption or purchase of ordinary shares), if the assets available for distribution amongst our shareholders shall be more than sufficient to repay the whole of the share capital at the commencement of the winding up, the surplus shall be distributed amongst our shareholders in proportion to the par value of the shares held by them at the commencement of the winding up, subject to a deduction from those shares in respect of which there are monies due, of all monies payable to our company for unpaid calls or otherwise. If our assets available for distribution are insufficient to repay all of the paid-up capital, the assets will be distributed so that the losses are borne by our shareholders in proportion to the par value of the shares held by them. Any distribution of assets or capital to a holder of ordinary shares will be the same in any liquidation event.

Calls on Ordinary Shares and Forfeiture of Ordinary Shares. Our board of directors may from time to time make calls upon shareholders for any amounts unpaid on their ordinary shares in a notice served to such shareholders at least 14 clear days prior to the specified time of payment. The ordinary shares that have been called upon and remain unpaid are subject to forfeiture.

Redemption, Repurchase and Surrender of Ordinary Shares. We may issue shares on terms that such shares are subject to redemption, at our option or at the option of the holders thereof, on such terms and in such manner as may be determined, before the issue of such shares, by our board of directors or by an ordinary resolution of our shareholders. Our company may also repurchase any of our shares provided that the manner and terms of such purchase have been approved by our board of directors or by an ordinary resolution of our shareholders, or are otherwise authorized by our post-offering memorandum and articles of association. Under the Companies Act, the redemption or repurchase of any share may be paid out of our company's profits or out of the proceeds of a fresh issue of shares made for the purpose of such redemption or repurchase, or out of capital (including share premium account and capital redemption reserve) if the Company can, immediately following such payment, pay its debts as they fall due in the ordinary course of business. In addition, under the Companies Act no such share may be redeemed or repurchased (a) unless it is fully paid up, (b) if such redemption or repurchase would result in there being no shares outstanding, or (c) if the company has commenced liquidation. In addition, our company may accept the surrender of any fully paid share for no consideration.

Variations of Rights of Shares. If at any time our share capital is divided into different classes or series of shares, the rights attached to any class or series of shares (unless otherwise provided by the terms of issue of the shares of that class or series), whether or not our company is being wound-up, may be varied with the consent in writing of holders of not less than a majority of the issued shares of that class or series or with the sanction of a special resolution at a separate meeting of the holders of the shares of the class or series. The rights conferred upon the holders of the shares of any class issued shall not, unless otherwise expressly provided by the terms of issue of the shares of that class, be deemed to be varied by the creation or issue of further shares ranking *pari passu* with such existing class of shares.

Inspection of Books and Records. Holders of our ordinary shares have no general right under Cayman Islands law to inspect or obtain copies of our list of shareholders or our corporate records. However, we will provide our shareholders with annual audited financial statements.

Issuance of Additional Shares. Our post-offering memorandum and articles of association authorizes our board of directors to issue additional ordinary shares from time to time as our board of directors shall determine, to the extent of available authorized but unissued shares.

Our post-offering memorandum and articles of association also authorizes our board of directors to establish from time to time one or more series of preferred shares and to determine, with respect to any series of preferred shares, the terms and rights of that series, including:

- the designation of the series;
- the number of shares of the series;
- the dividend rights, dividend rates, conversion rights, voting rights; and
- the rights and terms of redemption and liquidation preferences.

Our board of directors may issue preferred shares without action by our shareholders to the extent authorized but unissued. Issuance of these shares may dilute the voting power of holders of ordinary shares.

Anti-Takeover Provisions. Some provisions of our post-offering memorandum and articles of association may discourage, delay or prevent a change of control of our company or management that shareholders may consider favorable, including provisions that authorize our board of directors to issue preferred shares in one or more series and to designate the price, rights, preferences, privileges and restrictions of such preferred shares without any further vote or action by our shareholders.

Changes in Capital.

We may from time to time by ordinary resolution:

- increase the share capital by such sum, to be divided into shares of such classes and amount, as the resolution shall prescribe;
- consolidate and divide all or any of our share capital into shares of a larger amount than our existing shares;
- sub-divide our existing shares, or any of them into shares of a smaller amount; or
- cancel any shares which, at the date of the passing of the resolution, have not been taken or agreed to be taken by any person and diminish the amount of our share capital by the amount of the shares so canceled.

We may by special resolution, subject to any confirmation or consent required by the Companies Act, reduce our share capital or any capital redemption reserve in any manner permitted by law.

Exempted Company. We are an exempted company with limited liability under the Companies Act. The Companies Act distinguishes between ordinary resident companies and exempted companies. Any company that is registered in the Cayman Islands but conducts business mainly outside of the Cayman Islands may apply to be registered as an exempted company. The requirements for an exempted company are essentially the same as for an ordinary company except that an exempted company:

- does not have to file an annual return of its shareholders with the Registrar of Companies;
- is not required to open its register of members for inspection;
- does not have to hold an annual general meeting;
- may issue shares with no par value;
- may obtain an undertaking against the imposition of any future taxation (such undertakings are usually given for 30 years in the first instance);
- may register by way of continuation in another jurisdiction and be deregistered in the Cayman Islands;
- may register as a limited duration company; and
- may register as a segregated portfolio company.

“Limited liability” means that the liability of each shareholder is limited to the amount unpaid by the shareholder on that shareholder’s shares of the company.

Register of Members. Under the Companies Act, we must keep a register of members and there should be entered therein:

- the names and addresses of our members, and a statement of the shares held by each member, which shall include: (i) the amount paid or agreed to be considered as paid on the shares of each member, (ii) the number and category of shares held by each member, and (iii) whether each relevant category of shares held by a member carries voting rights under the post-offering memorandum and articles of association, and if so, whether such voting rights are conditional;

- the date on which the name of any person was entered on the register as a member; and

- the date on which any person ceased to be a member.

Under the Companies Act, the register of members of our company is prima facie evidence of the matters set out therein (that is, the register of members will raise a presumption of fact on the matters referred to above unless rebutted) and a member registered in the register of members is deemed as a matter of the Companies Act to have legal title to the shares as set against its name in the register of members. Upon completion of this offering, we will perform the procedure necessary to immediately update the register of members to record and give effect to the issuance of shares by us to the Depositary (or its nominee) as the depositary. Once our register of members has been updated, the shareholders recorded in the register of members will be deemed to have legal title to the shares set against their name.

If the name of any person is incorrectly entered in or omitted from our register of members, or if there is any default or unnecessary delay in entering on the register the fact of any person having ceased to be a member of our company, the person or member aggrieved (or any member of our company or our company itself) may apply to the Grand Court of the Cayman Islands for an order that the register be rectified, and the Court may either refuse such application or it may, if satisfied of the justice of the case, make an order for the rectification of the register.

10.C. Material Contracts

We have not entered into any material contracts other than in the ordinary course of business and other than those described in this annual report.

10.D. Exchange Controls

The Cayman Islands currently has no exchange control regulations or currency restrictions. For exchange control regulations or currency restrictions in China, see “Item 4 Information of the Company—B. Business Overview—Regulation—Regulations Relating to Foreign Exchange.”

10.E. Taxation

The following discussion of Cayman Islands, PRC and U.S. federal income tax consequences of the ownershihp and disposition of the ADSs or ordinary shares is based upon laws and relevant interpretations thereof in effect as of the date of this annual report, all of which are subject to change. This discussion does not deal with all possible tax consequences relating to the ownership and disposition of the ADSs or ordinary shares, such as the tax consequences under state, local and other tax laws.

Cayman Islands Taxation

According to Walkers (Hong Kong), our Cayman Islands counsel, the Cayman Islands currently levies no taxes on individuals or corporations based upon profits, income, gains or appreciation, and there is no taxation in the nature of inheritance tax or estate duty. There are no other taxes likely to be material to us or holders of our ADSs or ordinary shares levied by the government of the Cayman Islands, except for stamp duties which may be applicable on instruments executed in, or after execution brought within the jurisdiction of the Cayman Islands. The Cayman Islands is not party to any double tax treaties that are applicable to any payments made to or by our company. There are no exchange control regulations or currency restrictions in the Cayman Islands.

Payments of dividends and capital in respect of the ADSs or ordinary shares will not be subject to taxation in the Cayman Islands and no withholding will be required on the payment of a dividend or capital to any holder of the ADSs or ordinary shares, nor will gains derived from the disposal of the ADSs or ordinary shares be subject to Cayman Islands income or corporation tax.

Material PRC Income Tax Considerations

Under the PRC EIT Law, which became effective on January 1, 2008 and was amended on December 29, 2018, an enterprise established outside the PRC with "de facto management bodies" within the PRC is considered a "resident enterprise" for PRC enterprise income tax purposes and is generally subject to a uniform 25% enterprise income tax rate on its worldwide income. Under the implementation rules to the PRC EIT Law, a "de facto management body" is defined as a body that has material and overall management and control over the manufacturing and business operations, personnel and human resources, finances and properties of an enterprise.

In addition, the SAT Circular 82 issued by the SAT in April 2009 specifies that certain offshore incorporated enterprises controlled by PRC enterprises or PRC enterprise groups will be classified as PRC resident enterprises if the following are located or resident in the PRC: (a) senior management personnel and departments that are responsible for daily production, operation and management; (b) financial and personnel decision-making bodies; (c) key properties, accounting books, company seal, minutes of board meetings and shareholders' meetings; and (d) half or more of the senior management or directors having voting rights. Further to SAT Circular 82, the SAT issued the SAT Bulletin 45, which took effect in September 2011, to provide more guidance on the implementation of SAT Circular 82. SAT Bulletin 45 provides for procedures and administration details of determination on resident status and administration on post-determination matters. Our company is a company incorporated outside the PRC. As a holding company, its key assets are its ownership interests in its subsidiaries, and its key assets are located, and its records (including the resolutions of its board of directors and the resolutions of its shareholders) are maintained, outside the PRC. As such, we do not believe that our company meets all of the conditions above or is a PRC resident enterprise for PRC tax purposes. For similar reasons, we believe our other entities outside China are not PRC resident enterprises either. However, the tax resident status of an enterprise is subject to determination by the PRC tax authorities and uncertainties remain with respect to the interpretation of the term "de facto management body." There can be no assurance that the PRC government will ultimately take a view that is consistent with us. If the PRC tax authorities determine that our Cayman Islands holding company is a PRC resident enterprise for PRC enterprise income tax purposes, a number of unfavorable PRC tax consequences could follow. For example, a 10% withholding tax would be imposed on dividends we pay to our non-PRC enterprise shareholders (including our ADS holders). In addition, nonresident enterprise shareholders (including our ADS holders) may be subject to PRC tax on gains realized on the sale or other disposition of ADSs or ordinary shares, if such income is treated as sourced from within the PRC. Furthermore, if we are deemed a PRC resident enterprise, dividends paid to our non-PRC individual shareholders (including our ADS holders) and any gain realized on the transfer of ADSs or ordinary shares by such shareholders may be subject to PRC tax at a rate of 20% (which, in the case of dividends, may be withheld at source by us). These rates may be reduced by an applicable tax treaty, but it is unclear whether in practice non-PRC shareholders of our company would be able to obtain the benefits of any tax treaties between their country of tax residence and the PRC in the event that we are treated as a PRC resident enterprise. See "Item 3 Key Information—D. Risk Factors—Risks Related to Doing Business in the PRC—If we are classified as a PRC resident enterprise for PRC income tax purposes, such classification could result in unfavorable tax consequences to us and our non-PRC shareholders or ADS holders."

Material U.S. Federal Income Tax Considerations

The following discussion describes U.S. federal income tax consequences to the U.S. Holders described below of the ownership and disposition of the ADSs or ordinary shares. This discussion is not a comprehensive description of all of the tax considerations that may be relevant to your decision to hold the ADSs or ordinary shares. This discussion applies to you only if you are a U.S. Holder that holds the ADSs or underlying ordinary shares as capital assets for U.S. federal income tax purposes. In addition, it does not describe all of the tax consequences that may be relevant in light of your particular circumstances, including the alternative minimum tax, the Medicare contribution tax on net investment income, and tax consequences applicable to you if you are subject to special rules, such as:

- one of certain financial institutions;
- a dealer or trader in securities that uses a mark-to-market method of tax accounting;

- a person holding ADSs or ordinary shares as part of a straddle, conversion transaction, integrated transaction or similar transaction;
- a person whose functional currency for U.S. federal income tax purposes is not the U.S. dollar;
- an entity classified as a partnership for U.S. federal income tax purposes (and investors therein);
- a tax-exempt entity, “individual retirement account” or “Roth IRA’’;
- a person who acquired our ADSs or ordinary shares pursuant to the exercise of an employee stock option or otherwise as compensation;
- a person that owns or is deemed to own 10% or more of our stock by vote or value; or
- a person holding ADSs or ordinary shares in connection with a trade or business conducted outside the United States.

If you are a partnership for U.S. federal income tax purposes, the U.S. federal income tax consequences to your partners will generally depend on their status and your activities. Partnerships holding ADSs or ordinary shares and their partners should consult their tax advisors as to the particular U.S. federal income tax consequences of acquiring, owning or disposing of the ADSs or ordinary shares.

This discussion is based on the Internal Revenue Code of 1986, as amended, or the Code, administrative pronouncements, judicial decisions and final, temporary and proposed Treasury regulations, and the income tax treaty between the United States and the PRC, or the Treaty, all as of the date hereof, any of which is subject to change, possibly with retroactive effect.

For purposes of this discussion, you are a “U.S. Holder” if you are eligible for the benefits of the Treaty and are, for U.S. federal income tax purposes, a beneficial owner of ADSs or ordinary shares and:

- a citizen or individual resident of the United States;
- a corporation or other entity taxable as a corporation for U.S. federal income tax purposes, created or organized in or under the laws of the United States, any state therein or the District of Columbia; or
- an estate or trust the income of which is subject to U.S. federal income taxation regardless of its source.

Treasury regulations that apply to taxable years beginning on or after December 28, 2021 (the “Foreign Tax Credit Regulations”) may in some circumstances prohibit a U.S. person from claiming a foreign tax credit with respect to certain non-U.S. taxes that are not creditable under applicable income tax treaties. Accordingly, U.S. investors that are not eligible for Treaty benefits should consult their tax advisors regarding the creditability or deductibility of any PRC taxes imposed on dividends on, or dispositions of, the ADSs or ordinary shares. This discussion does not apply to investors in this special situation.

In general, if you own ADSs you will be treated as the owner of the underlying ordinary shares represented by those ADSs for U.S. federal income tax purposes. Accordingly, no gain or loss will be recognized if you exchange ADSs for the underlying ordinary shares represented by those ADSs.

Passive Foreign Investment Company Rules

In general, a non-U.S. corporation will be a passive foreign investment company, or a PFIC, for any taxable year in which (i) 75% or more of its gross income consists of passive income, or the income test, or (ii) 50% or more of the average value of its assets (generally determined on a quarterly basis) consists of assets that produce, or are held for the production of, passive income, or the asset test. For purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the ordinary shares of another corporation is treated as if it held its proportionate share of the assets of the other corporation and received directly its proportionate share of the income of the other corporation. Passive income generally includes interest, dividends, gains from certain property transactions, rents and royalties (other than certain rents or royalties derived in the active conduct of a trade or business). Cash is generally a passive asset for PFIC purposes. Goodwill is an active asset under the PFIC rules to the extent attributable to activities that produce active income.

The assets shown on our balance sheet are expected to consist primarily of cash and cash equivalents for the foreseeable future. Therefore, whether we will satisfy the asset test for any taxable year will depend largely on the value of our goodwill and on how quickly we utilize the cash in our business.

The value of our goodwill for any taxable year may be determined in large part by reference to the average of our market capitalization for that year. Because our market capitalization has generally declined substantially since our initial public offering (including in 2022 and recent months), if the value of our goodwill is determined by reference to the average of our quarterly market capitalization then it is our belief that we were likely a PFIC for our 2022 taxable year. Due to our declining market capitalization, there is a significant risk that we will also be a PFIC for 2023 and possibly future taxable years. In addition, the extent to which our goodwill should be characterized as a non-passive asset is not entirely clear. We have not obtained any valuation of our assets (including goodwill). U.S. Holders of our ADSs or ordinary shares should consult their tax advisors regarding the value and characterization of our assets for purposes of the PFIC rules, which are subject to some uncertainties.

If we are a PFIC for any taxable year and any of our subsidiaries is also a PFIC (any such entity, a “Lower-tier PFIC”), U.S. Holders will be deemed to own a proportionate amount (by value) of the shares of each Lower-tier PFIC and will be subject to U.S. federal income tax according to the rules described in the subsequent paragraph on (i) certain distributions by a Lower-tier PFIC and (ii) dispositions of shares of Lower-tier PFICs, in each case as if the U.S. Holders held such shares directly, even though the U.S. Holders will not receive the proceeds of those distributions or dispositions.

In general, if we are a PFIC for any taxable year during which a U.S. Holder holds our ADSs or ordinary shares, gain recognized by such U.S. Holder on a sale or other disposition (including certain pledges) of its ADSs or ordinary shares will be allocated ratably over that U.S. Holder’s holding period. The amounts allocated to the taxable year of the sale or disposition and to any year before we became a PFIC will be taxed as ordinary income. The amount allocated to each other taxable year will be subject to tax at the highest rate in effect for individuals or corporations, as appropriate, for that taxable year, and an interest charge will be imposed on the resulting tax liability for each such year. Furthermore, to the extent that distributions received by a U.S. Holder in any taxable year on its ADSs or ordinary shares exceed 125% of the average of the annual distributions on the ADSs or ordinary shares received during the preceding three taxable years or the U.S. Holder’s holding period, whichever is shorter, the excess distributions will be subject to taxation in the same manner.

Under a rule commonly referred to as the “once a PFIC, always a PFIC” rule, if we are a PFIC for any taxable year during which a U.S. Holder owns ADSs or ordinary shares, we will generally continue to be treated as a PFIC with respect to the U.S. Holder for all succeeding taxable years during which the U.S. Holder owns the ADSs or ordinary shares, even if we cease to meet the threshold requirements for PFIC status. If we are a PFIC for any taxable year but cease to be PFIC for subsequent years, U.S. Holders should consult their tax advisors regarding the advisability of making a “deemed sale” election that will allow them to eliminate the continuing PFIC status under certain circumstances, but may require them to recognize gain taxed under the general PFIC rules described in the preceding paragraph.

Alternatively, if we are a PFIC and if the ADSs are "regularly traded" on a "qualified exchange," a U.S. Holder of ADSs may make a mark-to-market election that will result in tax treatment different from the general tax treatment for PFICs described above. The ADSs will be treated as "regularly traded" for any calendar year in which more than a *de minimis* quantity of the ADSs are traded on a qualified exchange on at least 15 days during each calendar quarter. The Nasdaq Global Market, where the ADSs are listed, is a qualified exchange for this purpose, but there is no assurance that our ADSs will be treated as regularly traded for any relevant period. If a U.S. Holder makes the mark-to-market election, the U.S. Holder generally will recognize as ordinary income any excess of the fair market value of the ADSs at the end of each taxable year over their adjusted tax basis, and will recognize an ordinary loss in respect of any excess of the adjusted tax basis of the ADSs over their fair market value at the end of the taxable year (but only to the extent of the net amount of income previously included as a result of the mark-to-market election). If a U.S. Holder makes the election, the U.S. Holder's tax basis in the ADSs will be adjusted to reflect the income or loss amounts recognized. Any gain recognized on the sale or other disposition of ADSs in a taxable year in which we are a PFIC will be treated as ordinary income, and any loss will be treated as an ordinary loss (but only to the extent of the net amount of income previously included as a result of the mark-to-market election, with any excess treated as capital loss). If a U.S. Holder makes the mark-to-market election, distributions paid on ADSs will be treated as discussed under "—Taxation of Distributions" below (but subject to the discussion in the immediately subsequent paragraph). If we are a PFIC for any taxable year, U.S. Holders should consult their tax advisors regarding the availability and advisability of making a mark-to-market election in their particular circumstances. In particular, U.S. Holders should consider carefully the impact of a mark-to-market election with respect to their ADSs because we may have Lower-tier PFICs for which a mark-to-market election likely cannot be made.

The favorable tax rates for dividends paid to certain non-corporate U.S. Holders of ADSs, which are discussed below, do not apply to dividends from a corporation that is a PFIC in the year the dividend is paid or the preceding year. We do not intend to provide information necessary for U.S. Holders to make a "qualified electing fund election," which, if available, would result in tax treatment different from the tax treatment for PFICs described above.

If we are a PFIC for any taxable year during which a U.S. Holder owns any ADSs or ordinary shares, the U.S. Holder will generally be required to file annual reports with the Internal Revenue Service (the "IRS"). U.S. Holders should consult their tax advisors regarding the PFIC rules and their application.

Taxation of Distributions

The following is subject to the discussion under *"—Passive Foreign Investment Company Rules"* above.

Distributions paid on ADSs or ordinary shares, other than certain pro rata distributions of ordinary shares, will generally be treated as dividends to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Because we do not maintain calculations of our earnings and profits under U.S. federal income tax principles, we expect that any distributions will be reported to you as dividends. Dividends will not be eligible for the dividends-received deduction generally available to U.S. corporations under the Code. Subject to applicable limitations, dividends paid by "qualified foreign corporations" to certain non-corporate U.S. Holders are taxable at the favorable rates applicable to long-term capital gains. A non-U.S. corporation is generally treated as a qualified foreign corporation with respect to dividends paid on stock that is readily tradable on a securities market in the United States, such as the Nasdaq Global Market, where the ADSs are listed, or where the non-U.S. corporation is eligible for benefits of a comprehensive income tax treaty with the United States. Therefore such favorable rates may apply for so long as our ADSs are listed on the Nasdaq Global Market or if in the future we are eligible for benefits under the Treaty. However, as discussed above, the favorable rates do not apply if we are (or are treated with respect to a U.S. Holder as) a PFIC for the taxable year in which the dividend is paid or the preceding taxable year. Non-corporate U.S. Holders should consult their tax advisors to determine whether the favorable rate will apply to dividends they receive and whether they are subject to any special rules that limit their ability to be taxed at this favorable rate.

Dividends will be treated as foreign-source income for foreign tax credit purposes. As described in "—Material PRC Income Tax Considerations," dividends paid by us may be subject to PRC withholding tax. For U.S. federal income tax purposes, the amount of the dividend income will include any amounts withheld in respect of PRC withholding tax. Subject to applicable limitations, which vary depending upon your circumstances, PRC taxes withheld from dividend payments (at a rate not exceeding the applicable rate provided in the Treaty) generally will be creditable against your U.S. federal income tax liability. In lieu of claiming a credit, you may elect to deduct creditable PRC taxes in computing your taxable income, subject to applicable limitations. An election to deduct foreign taxes instead of claiming foreign tax credits must apply to all creditable foreign taxes paid or accrued in the taxable year. The rules governing foreign tax credits are complex, and you should consult your tax advisors regarding the creditability of foreign tax credits in your particular circumstances.

Sale or Other Disposition of ADSs or Ordinary Shares

The following is subject to the discussion under *"—Passive Foreign Investment Company Rules"* above.

Gain or loss realized on the sale or other taxable disposition of ADSs or ordinary shares will be capital gain or loss, and will be long-term capital gain or loss if you held the ADSs or ordinary shares for more than one year. The amount of the gain or loss will equal the difference between your tax basis in the ADSs or ordinary shares disposed of and the amount realized on the disposition, in each case as determined in U.S. dollars. This gain or loss will generally be U.S.-source gain or loss for foreign tax credit purposes. The deductibility of capital losses is subject to limitations.

As described in "—Material PRC Income Tax Considerations" above, gains on the sale of ADSs or ordinary shares may be subject to PRC taxes. Under the Code, capital gains of U.S. persons are generally treated as U.S.-source income. However, you may be able to elect to treat the gain as foreign-source income under the Treaty and claim foreign tax credit in respect of any PRC tax on dispositions. The Foreign Tax Credit Regulations generally preclude you from claiming a foreign tax credit with respect to PRC income taxes on gains from dispositions of ADSs or ordinary shares if you do not elect to apply the benefits of the Treaty. However, in that case it is possible that any PRC taxes on disposition gains may either be deductible or reduce the amount realized on the disposition. The rules governing foreign tax credits and deductibility of foreign taxes are complex. You should consult your tax advisor regarding the consequences of the imposition of any PRC tax on disposition gains, including the Treaty's resourcing rule, any reporting requirements with respect to a Treaty-based return position and the creditability or deductibility of the PRC tax on disposition gains in your particular circumstances (including any applicable limitations).

Information Reporting and Backup Withholding

Payments of dividends and sales proceeds from the sale or exchange of our ADSs or ordinary shares that are made within the United States or through certain U.S.-related financial intermediaries generally are subject to information reporting, and may be subject to backup withholding, unless (i) you are a corporation or other exempt recipient or (ii) in the case of backup withholding, you provide a correct taxpayer identification number and certify that you are not subject to backup withholding. Backup withholding is not an additional tax. The amount of any backup withholding from a payment to you will be allowed as a credit against your U.S. federal income tax liability and may entitle you to a refund, provided that the required information is timely furnished to the IRS.

Certain U.S. Holders who are individuals (and certain specified entities) may be required to report information relating to their ownership of ordinary shares, or non-U.S. accounts through which ADSs or ordinary shares are held. You should consult your tax advisor regarding your reporting obligations with respect to the ADSs or ordinary shares.

10.F. Dividends and Paying Agents

Not applicable.

10.G. Statement by Experts

Not applicable.

10.H. Documents on Display

We previously filed with the SEC registration statement on Form F-1 (File Number 333-252210), as amended, including annual report contained therein, to register our ordinary shares in relation to our initial public offering. We also filed with the SEC related registration statement on Form F-6 (File Number 333-252543) to register the ADSs.

We are subject to the periodic reporting and other informational requirements of the Exchange Act as applicable to foreign private issuers. Under the Exchange Act, we are required to file reports and other information with the SEC. Specifically, we are required to file annually a Form 20-F within four months after the end of each fiscal year. Copies of reports and other information, when so filed with the SEC, can be inspected and copied at the public reference facilities maintained by the SEC at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You can request copies of these documents, upon payment of a duplicating fee, by writing to the SEC. The public may obtain information regarding the Washington, D.C. Public Reference Room by calling the Commission at 1-800-SEC-0330. The SEC also maintains a web site at www.sec.gov that contains reports, proxy and information statements, and other information regarding registrants that make electronic filings with the SEC using its EDGAR system. As a foreign private issuer, we are exempt from the rules of the Exchange Act prescribing the furnishing and content of quarterly reports and proxy statements, and our executive officers, directors and principal shareholders are exempt from the reporting and short-swing profit recovery provisions contained in Section 16 of the Exchange Act. In addition, we are not required under the Exchange Act to file periodic reports and financial statements with the SEC as frequently or as promptly as U.S. companies whose securities are registered under the Exchange Act.

We will furnish JPMorgan Chase Bank, N.A., the depositary of our ADSs, with our annual reports, which will include a review of operations and annual audited consolidated financial statements, and all notices of shareholders' meetings and other reports and communications that are made generally available to our shareholders. The depositary will make such notices, reports and communications available to holders of ADSs and, upon our request, will mail to all record holders of ADSs the information contained in any notice of a shareholders' meeting received by the depositary from us.

10.I. Subsidiary Information

Not applicable.

10.J. Annual Report to Security Holders

Not applicable.

ITEM 11. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Interest rate risk

Our exposure to interest rate risk primarily relates to the interest income generated by excess cash, which is mostly held in interest-bearing bank deposits. We have not used any derivative financial instruments to manage our interest risk exposure. Interest-earning instruments carry a degree of interest rate risk. We have not been exposed, nor do we anticipate being exposed, to material risks due to changes in interest rates. However, our future interest income may be lower than expected due to changes in market interest rates.

Foreign exchange risk

We are a global business enterprise with part of our operations based in the PRC. A part of our transactions were settled in Renminbi, and our financial statements are presented in U.S. dollars. We do not believe that we currently have any significant direct foreign exchange risk and have not used any derivative financial instruments to hedge our exposure to such risk. Although, in general, our exposure to foreign exchange risks should be limited, the value of your investment in the ADSs will be affected by the exchange rate between U.S. dollar and Renminbi because a portion of value of our business is effectively denominated in Renminbi, while the ADSs representing our ordinary shares will be traded in U.S. dollars.

The value of the Renminbi against the U.S. dollar and other currencies is affected by changes in China's political and economic conditions and by China's foreign exchange policies, among other things. In July 2005, the PRC government changed its decades-old policy of pegging the value of the Renminbi to the U.S. dollar, and the Renminbi appreciated more than 20% against the U.S. dollar over the following three years. Between July 2008 and June 2010, this appreciation subsided and the exchange rate between the Renminbi and the U.S. dollar remained within a narrow band. Since June 2010, the Renminbi has fluctuated against the U.S. dollar, at times significantly and unpredictably. While appreciating approximately by 7% against the U.S. dollar in 2017, the Renminbi in 2018 depreciated approximately by 5% against the U.S. dollar. Since October 1, 2016, the Renminbihas joined the International Monetary Fund (IMF)'s basket of currencies that make up the Special Drawing Right (SDR), along with the U.S. dollar, the Euro, the Japanese yen and the British pound. With the development of the foreign exchange market and progress towards interest rate liberalization and Renminbi internationalization, the PRC government may in the future announce further changes to the exchange rate system and there is no guarantee that the RMB will not appreciate or depreciate significantly in value against the U.S. dollar in the future. It is difficult to predict how market forces or PRC or U.S. government policy may impact the exchange rate between the Renminbi and the U.S. dollar in the future.

To the extent that we need to convert U.S. dollars into Renminbi for our operations, appreciation of Renminbi against the U.S. dollar would reduce the Renminbi amount we receive from the conversion. Conversely, if we decide to convert Renminbi into U.S. dollars for the purpose of making payments for dividends on our ordinary shares or ADSs, servicing our outstanding debt, or for other business purposes, appreciation of the U.S. dollar against the Renminbi would reduce the U.S. dollar amounts available to us.

Inflation risk

Since our inception, inflation in China has not materially impacted our results of operations. According to the National Bureau of Statistics of China, the year-over-year percent changes in the consumer price index for December 2020, 2021 and 2022 were increases of 2.4%, 0.9% and 2.0%, respectively. Although we have not in the past been materially affected by inflation since our inception, we can provide no assurance that we will not be affected in the future by higher rates of inflation in China.

ITEM 12. DESCRIPTION OF SECURITIES OTHER THAN EQUITY SECURITIES

12.A. Debt Securities

Not applicable.

12.B. Warrants and Rights

Not applicable.

12.C. Other Securities

Not applicable.

12.D. American Depositary Shares

Fees and Expense

The depositary may charge each person to whom ADSs are issued, including, without limitation, issuances against deposits of shares, issuances in respect of share distributions, rights and other distributions, issuances pursuant to a stock dividend or stock split declared by us or issuances pursuant to a merger, exchange of securities or any other transaction or event affecting the ADSs or deposited securities, and each person surrendering ADSs for withdrawal of deposited securities or whose ADRs are cancelled or reduced for any other reason, $5.00 for each 100 ADSs (or any portion thereof) issued, delivered, reduced, cancelled or surrendered, or upon which a share distribution or elective distribution is made or offered, as the case may be. The depositary may sell (by public or private sale) sufficient securities and property received in respect of a share distribution, rights and/or other distribution prior to such deposit to pay such charge.

The following additional charges shall also be incurred by the ADR holders, the beneficial owners, by any party depositing or withdrawing shares or by any party surrendering ADSs and/or to whom ADSs are issued (including, without limitation, issuance pursuant to a stock dividend or stock split declared by us or an exchange of stock regarding the ADSs or the deposited securities or a distribution of ADSs), whichever is applicable:

- a fee of U.S.$1.50 per ADR or ADRs for transfers of certificated or direct registration ADRs;
- a fee of U.S.$0.05 or less per ADS held for any cash distribution made, or for any elective cash/ stock dividend offered, pursuant to the deposit agreement;
- an aggregate fee of U.S.$0.05 or less per ADS per calendar year (or portion thereof) for services performed by the depositary in administering the ADRs (which fee may be charged on a periodic basis during each calendar year and shall be assessed against holders of ADRs as of the record date or record dates set by the depositary during each calendar year and shall be payable in the manner described in the next succeeding provision);
- a fee for the reimbursement of such fees, charges and expenses as are incurred by the depositary and/or any of its agents (including, without limitation, the custodian and expenses incurred on behalf of ADR holders in connection with compliance with foreign exchange control regulations or any law or regulation relating to foreign investment) in connection with the servicing of the shares or other deposited securities, the sale of securities (including, without limitation, deposited securities), the delivery of deposited securities or otherwise in connection with the depositary's or its custodian's compliance with applicable law, rule or regulation (which fees and charges shall be assessed on a proportionate basis against ADR holders as of the record date or dates set by the depositary and shall be payable at the sole discretion of the depositary by billing such ADR holders or by deducting such charge from one or more cash dividends or other cash distributions);
- a fee for the distribution of securities (or the sale of securities in connection with a distribution), such fee being in an amount equal to the $0.05 per ADS issuance fee for the execution and delivery of ADSs which would have been charged as a result of the deposit of such securities (treating all such securities as if they were shares) but which securities or the net cash proceeds from the sale thereof are instead distributed by the depositary to those ADR holders entitled thereto;
- stock transfer or other taxes and other governmental charges;
- cable, telex and facsimile transmission and delivery charges incurred at your request in connection with the deposit or delivery of shares, ADRs or deposited securities;
- transfer or registration fees for the registration of transfer of deposited securities on any applicable register in connection with the deposit or withdrawal of deposited securities; and
- fees of any division, branch or affiliate of the depositary utilized by the depositary to direct, manage and/or execute any public and/or private sale of securities under the deposit agreement.

To facilitate the administration of various depositary receipt transactions, including disbursement of dividends or other cash distributions and other corporate actions, the depositary may engage the foreign exchange desk within JPMorgan Chase Bank, N.A. (the "Bank") and/or its affiliates in order to enter into spot foreign exchange transactions to convert foreign currency into U.S. dollars. For certain currencies, foreign exchange transactions are entered into with the Bank or an affiliate, as the case may be, acting in a principal capacity. For other currencies, foreign exchange transactions are routed directly to and managed by an unaffiliated local custodian (or other third party local liquidity provider), and neither the Bank nor any of its affiliates is a party to such foreign exchange transactions.

The foreign exchange rate applied to a foreign exchange transaction will be either (a) a published benchmark rate, or (b) a rate determined by a third party local liquidity provider, in each case plus or minus a spread, as applicable. The depositary will disclose which foreign exchange rate and spread, if any, apply to such currency on the "Disclosures" page (or successor page) of ADR.com. Such applicable foreign exchange rate and spread may (and neither the depositary, the Bank nor any of their affiliates is under any obligation to ensure that such rate does not) differ from rates and spreads at which comparable transactions are entered into with other customers or the range of foreign exchange rates and spreads at which the Bank or any of its affiliates enters into foreign exchange transactions in the relevant currency pair on the date of the foreign exchange transaction. Additionally, the timing of execution of a foreign exchange transaction varies according to local market dynamics, which may include regulatory requirements, market hours and liquidity in the foreign exchange market or other factors. Furthermore, the Bank and its affiliates may manage the associated risks of their position in the market in a manner they deem appropriate without regard to the impact of such activities on the depositary, us, holders or beneficial owners. *The spread applied does not reflect any gains or losses that may be earned or incurred by the Bank and its affiliates as a result of risk management or other hedging related activity.*

Notwithstanding the foregoing, to the extent we provide U.S. dollars to the depositary, neither the Bank nor any of its affiliates will execute a foreign exchange transaction as set forth herein. In such case, the depositary will distribute the U.S. dollars received from us.

Further details relating to the applicable foreign exchange rate, the applicable spread and the execution of foreign exchange transactions will be provided by the depositary on ADR.com. Each holder and beneficial owner by holding or owning an ADR or ADS or an interest therein, and we, each acknowledge and agree that the terms applicable to foreign exchange transactions disclosed from time to time on ADR.com will apply to any foreign exchange transaction executed pursuant to the deposit agreement.

We will pay all other charges and expenses of the depositary and any agent of the depositary (except the custodian) pursuant to agreements from time to time between us and the depositary.

The right of the depositary to receive payment of fees, charges and expenses survives the termination of the deposit agreement, and shall extend for those fees, charges and expenses incurred prior to the effectiveness of any resignation or removal of the depositary.

The fees and charges described above may be amended from time to time by agreement between us and the depositary.

The depositary may make available to us a set amount or a portion of the depositary fees charged in respect of the ADR program or otherwise upon such terms and conditions as we and the depositary may agree from time to time. The depositary collects its fees for issuance and cancellation of ADSs directly from investors depositing shares or surrendering ADSs for the purpose of withdrawal or from intermediaries acting for them. The depositary collects fees for making distributions to investors by deducting those fees from the amounts distributed or by selling a portion of distributable property to pay the fees. The depositary may collect its annual fee for depositary services by deduction from cash distributions, or by directly billing investors, or by charging the book-entry system accounts of participants acting for them. The depositary will generally set off the amounts owing from distributions made to holders of ADSs. If, however, no distribution exists and payment owing is not timely received by the depositary, the depositary may refuse to provide any further services to ADR holders that have not paid those fees and expenses owing until such fees and expenses have been paid. At the discretion of the depositary, all fees and charges owing under the deposit agreement are due in advance and/or when declared owing by the depositary.

Payments by Depositary

Our depositary anticipates to reimburse us for certain expenses we incur in respect of the ADR program established pursuant to the Deposit Agreement, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise, upon such terms and conditions as the Depositary agrees with us from time to time. As of the date of this annual report, we have not received such reimbursement from the depositary.

PART II

ITEM 13. DEFAULTS, DIVIDEND ARREARAGES AND DELINQUENCIES

None.

ITEM 14. MATERIAL MODIFICATIONS TO THE RIGHTS OF SECURITY HOLDERS AND USE OF PROCEEDS

14.A. — 14.D. Material Modifications to the Rights of Security Holders

See “Item 10 Additional Information” for a description of the rights of shareholders, which remain unchanged.

14.E. Use of Proceeds

The following “Use of Proceeds” information relates to the registration statement on Form F-1, as amended (File No. 333- 252210) in relation to our initial public offering, which was declared effective by the SEC on February 8, 2021. In February 2021, we completed our initial public offering in which we issued and sold an aggregate of 8,457,100 ADSs, representing 10,571,375 ordinary shares, resulting in net proceeds to us of approximately US$145.9 million, net of the underwriting discounts and commissions and other fees paid or payable by us in connection with the offering.

The F-1 Registration Statement was declared effective by the SEC on February 8, 2021. The total expenses incurred for our company’s account in connection with our initial public offering was approximately US$15.1 million, which included US$11.2 million in underwriting discounts and commissions for the initial public offering and approximately US$3.6 million in other costs and expenses for our initial public offering. We received net proceeds of approximately US$145.9 million from our initial public offering. None of the transaction expenses included payments to directors or officers of our company or their associates, persons owning more than 10% or more of our equity securities or our affiliates. None of the net proceeds from the initial public offering were paid, directly or indirectly, to our directors or officers and persons owning 10% or more of our equity securities or our affiliates.

For the period from the effective date of the registration statement on Form F-1 to December 31, 2022, we used US$64 million of the net proceeds received from our initial public offering primarily for research and development of our product candidates. We still intend to use the remainder of the proceeds from our initial public offering as disclosed in our registration statements on Form F-1.

ITEM 15. CONTROLS AND PROCEDURES

Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, has performed an evaluation of the effectiveness of our disclosure controls and procedures (as defined in Rule 13a-15(e) under the Exchange Act) as of the end of the period covered by this report, as required by Rule 13a-15(b) under the Exchange Act.

Based upon that evaluation, our management has concluded that, as of December 31, 2022, our disclosure controls and procedures were effective in ensuring that the information required to be disclosed by us in the reports that we file or submit under the Exchange Act was recorded, processed, summarized and reported, within the time periods specified in the SEC’s rules and forms, and that the information required to be disclosed by us in the reports that we file or submit under the Exchange Act is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, to allow timely decisions regarding required disclosure.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. As required by Rule 13a-15(c) of the Exchange Act, our management conducted an evaluation of our company's internal control over financial reporting as of December 31, 2022 based on the framework in Internal Control—Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on this evaluation, our management concluded that our internal control over financial reporting was effective as of December 31, 2022.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness of our internal control over financial reporting to future periods are subject to the risks that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Attestation Report of the Registered Public Accounting Firm

This annual report on Form 20-F does not include an attestation report of our registered public accounting firm due to a transition period established by rules of the SEC for newly public companies.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the period covered by this annual report on Form 20-F that have materially affected, or that are reasonably likely to materially affect, our internal control over financial reporting.

Item 16.A. Audit Committee Financial Expert

Our Board of Directors has determined that Mr. Andy (Yiu Leung) Cheung, an independent director and the chairperson of our audit committee, qualifies as an "audit committee financial expert" within the meaning of the SEC rules and in accordance with applicable Nasdaq Global Market standards. Mr. Andy (Yiu Leung) Cheung satisfies the "independence" requirements of Rule 10A-3 under the Securities Exchange Act of 1934, as amended, and the applicable Nasdaq Global Market standards.

Item 16.B. Code of Ethics

Our Board of Directors has adopted a code of business conduct and ethics that applies to all of our directors, officers, employees, including certain provisions that specifically apply to our principal executive officer, principal financial officer, principal accounting officer or controller and any other persons who perform similar functions for us. We have filed our code of business conduct and ethics as Exhibit 99.1 of our registration statement on Form F-1 (File No. 333- 252210), as amended, filed with the SEC on January 19, 2021 and posted a copy of our code of business conduct and ethics on our website at *http://investor.adagene.com*. We hereby undertake to provide to any person without charge, a copy of our code of business conduct and ethics within ten working days after we receive such person's written request.

Item 16.C. Principal Accountant Fees and Services

Auditor Fees

The following table sets forth the aggregate fees by categories specified below in connection with certain professional services rendered by PricewaterhouseCoopers Zhong Tian LLP, our independent registered public accounting firm, for the periods indicated.

	Year Ended December 31,	
	2021	2022
	RMB	RMB
	(in thousands)	
Services		
Audit Fees(1)	5,800	5,800
Audit-Related Fees(2)	0	0
Tax Fees(3)	0	0
Other Fees(4)	0	0
Total	5,800	5,800

(1) *Audit Fees*. Audit fees mean the aggregate fees billed in each of the fiscal periods listed for professional services rendered by our principal auditors for the audit of our annual consolidated financial statements and assistance with and review of documents filed with the SEC.
(2) *Audit-related Fees*. Audit-related fees mean the aggregate fees billed for professional services rendered by our principal auditors for the assurance and related services, which were not included under Audit Fees above.
(3) *Tax Fees*. Tax fees mean fees incurred from professional services related to tax compliance.
(4) *Other Fees*. Other fees mean fees incurred from professional services related to training, advisory and assurance for corporate and social responsibility reporting and professional services related to tax advice.

The policy of our audit committee is to pre-approve all audit and non-audit services provided by PricewaterhouseCoopers Zhong Tian LLP, our independent registered public accounting firm, including audit services and audit-related services as described above, other than those for *de minimis* services which are approved by the audit committee prior to the completion of the audit.

16.D. Exemptions from the Listing Standards for Audit Committees

Not applicable.

16.E. Purchases of Equity Securities by the Issuer and Affiliated Purchasers

On July 7, 2021, our board of directors authorized a share repurchase program whereby our company was authorized a share repurchase program under which the Company may repurchase up to US$20.0 million of its ordinary shares in the form of American depositary shares during a period of up to 12 months commencing on July 20, 2021 (the “2021 Share Repurchase Program”).

The Company’s share repurchases may be made from time to time on the open market at prevailing market prices, in open-market transactions, privately negotiated transactions or block trades, and/or through other legally permissible means, depending on market conditions and in accordance with the applicable rules and regulations. The timing and conditions of the share repurchases will be subject to various factors including the requirements under Rule 10b-18 and Rule 10b5-1 of the Exchange Act. Our board of directors will review the share repurchase program periodically and may authorize adjustments to its terms and size or suspend or discontinue the program.

The following table summarizes the details of the repurchases made in accordance with the 2021 Share Repurchase Program from April 1, 2022 to July 19, 2022:

Period	Total Number of ADSs Purchased	Average Price Paid Per ADS[1]	Total Number of ADSs Purchased as Part of the Publicly Announced Plan	Approximate Dollar Value of ADSs that May Yet Be Purchased Under the Plan (US$in thousand)
April 2022	195,788	$ 3.7	730,595	$ 15,259
May 2022	102,689	$ 3.1	833,284	$ 14,936
June 2022	190,083	$ 2.2	1,023,367	$ 14,513
July 1 - 19, 2022	383,218	$ 2.0	1,406,585	$ 13,731
Total	**871,778**	**$ 2.6**	**1,406,585**	**$ 13,731**

Notes:

(1) Each ADS representing one and one quarter ordinary shares. Average price paid per ADS is calculated using the execution price for each repurchase excluding commissions paid to the broker.

On June 29, 2022, our board of directors authorized a share repurchase program whereby our company was authorized a share repurchase program under which the Company may repurchase up to US$10.0 million of its ordinary shares in the form of American depositary shares during a period of up to 12 months commencing on July 20, 2022 (the “2022 Share Repurchase Program”). The 2022 Share Repurchase Program was subsequently terminated in July 2022.

The Company’s share repurchases may be made from time to time on the open market at prevailing market prices, in open-market transactions, privately negotiated transactions or block trades, and/or through other legally permissible means, depending on market conditions and in accordance with the applicable rules and regulations. The timing and conditions of the share repurchases will be subject to various factors including the requirements under Rule 10b-18 and Rule 10b5-1 of the Exchange Act. Our board of directors will review the share repurchase program periodically and may authorize adjustments to its terms and size or suspend or discontinue the program.

The following table summarizes the details of the repurchases made in accordance with the 2022 Share Repurchase Program from July 20, 2022 to July 31, 2022:

Period	Total Number of ADSs Purchased	Average Price Paid Per ADS[1]	Total Number of ADSs Purchased as Part of the Publicly Announced Plan	Approximate Dollar Value of ADSs that May Yet Be Purchased Under the Plan (US$ in thousand)
July 20 – 31, 2022				
Total	**39,900**	**$ 1.8**	**39,900**	**$ 9,928**

Notes:

(1) Each ADS representing one and one quarter ordinary shares. Average price paid per ADS is calculated using the execution price for each repurchase excluding commissions paid to the broker.

16.F. Change in Registrant’s Certifying Accountant

Not applicable.

16.G. Corporate Governance

As a Cayman Islands exempted company listed on Nasdaq Stock Market, we are subject to the Nasdaq corporate governance listing standards. However, Rule 5615 of the Nasdaq Rules permits a foreign private issuer like our company to follow home country practice in lieu of certain corporate governance matters as required under Rule 5600 Series, Rule 5250(b)(3) and Rule 5250(d) of the Nasdaq Rules.

Certain corporate governance practices in the Cayman Islands, which is our home country, may differ significantly from the Nasdaq corporate governance listing standards. We elect to rely on home country practice exemption in lieu of the requirements of the Rule 5600 Series of the Nasdaq Rules, except the following: compliance with the Notification of Noncompliance requirement (Rule 5625), the Voting Rights requirement (Rule 5640), the Diverse Board Representation Rule (Rule 5605(f)), the Board Diversity Disclosure Rule (Rule 5606), having an audit committee that satisfies Rule 5605(c)(3), and ensuring that such audit committee's members meet the independence requirement in Rule 5605(c)(2)(A)(ii).

In particular, we relied on home country practice exemption with respect to Rule 5620(a) of the Nasdaq Rules, which requires a Nasdaq-listed company to hold an annual meeting of Shareholders no later than one year after the end of the company's fiscal year-end and we did not hold an annual shareholders meeting in 2021. We may, however, hold annual shareholder meetings in the future if there are significant issues that require shareholders' approvals.

We elected to follow home country practice exemption and be exempt from the requirements to obtain shareholder approval for (1) certain acquisitions of the stock or assets of another company under Rule 5635(a) of the Nasdaq Rules, (2) the issuance of securities when the issuance or potential issuance will result in a change of control of the Company under Rule 5635(b) of the Nasdaq Rules, (3) the issuance of securities when a stock option or purchase plan is to be established or materially amended or other equity compensation arrangement made or materially amended under Rule 5635(c) of the Nasdaq Rules, and (4) the issuance of 20% or more of its outstanding ordinary shares under Rule 5635(d) of the Nasdaq Rules.

We relied on our home country practice exemption with respect to Rule 5605(d)(2) of the Nasdaq Rules, which requires a Nasdaq-listed company to establish a compensation committee comprised entirely of independent directors and two out of three members of our compensation committee are independent directors. We relied on our home country practice exemption with respect to Rule 5605(e)(1) of the Nasdaq Rules, which requires a Nasdaq-listed company to nominate director nominees either by a majority independent board or by a nominations committee comprised solely of independent directors and we do not have a majority independent board or a nominations committee comprised solely of independent directors. We relied on our home country practice exemption with respect to Rule 5250(b)(3) of the Nasdaq Rules, which requires a Nasdaq-listed company to disclose third party director and nominee compensation no later than when the companies files its next Form 20-F and we did not disclose such information in the form of 20-F for the year of 2020,2021 and 2022. We may also opt to rely on additional home country practice exemptions in the future.

Walkers (Hong Kong), our Cayman Islands counsel, has provided a letter to the Nasdaq Stock Market certifying that under Cayman Islands law, we are not required to comply with abovementioned requirements.

Our shareholders may be afforded less protection than they otherwise would under the Nasdaq Global Market corporate governance listing standards applicable to U.S. domestic issuers. See "Item 3 Key Information—D. Risk Factors—Risks Related to the ADSs—As an exempted company incorporated in the Cayman Islands, we are permitted to adopt certain home country practices in relation to corporate governance matters that differ significantly from the Nasdaq listing standards; these practices may afford less protection to shareholders than they would enjoy if we complied fully with the Nasdaq listing standards."

16.H. Mine Safety Disclosure

Not applicable.

16.I. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

(a) We have electronically submitted to the SEC on a supplemental basis documentation that establishes that Adagene Inc. is not owned or controlled by a governmental entity in the foreign jurisdiction.

(b) For the immediately preceding annual financial statement period, our auditor, which was a registered public accounting firm that the PCAOB was unable to inspect or investigate completely because of a position taken by the PRC government, issued our audit report that was included in our Form 20-F for the fiscal year of 2021.

As of the date of this annual report and to our best knowledge:

(i) none of our shares are owned by governmental entities in the jurisdiction in which we are incorporated or otherwise organized;

(ii) none of the governmental entities in the applicable foreign jurisdiction with respect to our registered public accounting firm have a controlling financial interest in us;

(iii) none of the members of our board of directors or the board of directors of our operating entity is an official of the Chinese Communist Party; and

(iv) our amended and restated memorandum and articles of association does not contain any charter of the Chinese Communist Party.

16.J. Insider Trading Policies

(a) We have adopted insider trading policies and procedures governing the purchase, sale, and other dispositions of our securities by directors, senior management, and employees that are reasonably designed to promote compliance with applicable insider trading laws, rules and regulations, and any listing standards applicable to us.

(b) [Not applicable.]

PART III

ITEM 17. FINANCIAL STATEMENTS

We have elected to provide financial statements pursuant to Item 18.

ITEM 18. FINANCIAL STATEMENTS

Our consolidated financial statements are included at the end of this annual report.

ITEM 19. EXHIBITS

Exhibit Number	Description of Document
1.1	Seventh Amended and Restated Memorandum and Articles of Association of the Registrant, as currently effective (incorporated by reference to Exhibit 3.2 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
2.1	Form of Registrant's Specimen American Depositary Receipt ((incorporated by reference to Exhibit 4.3 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021))
2.2	Registrant's Specimen Certificate for Ordinary Shares (incorporated by reference to Exhibit 4.2 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
2.3	Form of Deposit Agreement between the Registrant, the depositary and holders of the American Depositary Shares (incorporated by reference to Exhibit 4.3 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
2.4	Fifth Amended and Restated Shareholders Agreement by and among Adagene Inc. and shareholders of Adagene Inc. named therein dated December 19, 2019 (incorporated by reference to Exhibit 4.4 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
2.5*	Description of Registrant's Securities
4.1	Fourth Amended and Restated Right of First Refusal and Co-Sale Agreement by and between Adagene Inc., non-investor shareholders and investors named therein dated December 19, 2019 (incorporated by reference to Exhibit 4.5 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
4.2	Adagene Inc. Second Amended and Restated Share Incentive Plan (incorporated by reference to Exhibit 10.1 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
4.3	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers (incorporated by reference to Exhibit 10.2 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
4.4	Form of Employment Agreement between the Registrant and an executive officer of the Registrant (incorporated by reference to Exhibit 10.3 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
4.5	Adagene Inc. 2021 Performance Incentive Plan (incorporated by reference to Exhibit 10.13 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
4.6	Collaboration and License Agreement between Exelixis, Inc. and Adagene Incorporated dated February 1, 2021 (incorporated by reference to Exhibit 10.14 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
4.7 † #	Collaboration and License Agreement between Adagene Incorporated and Genzyme Corporation dated February 25, 2022 (incorporated by reference to Exhibit 4.16 from our annual report for the year of 2021, filed with the SEC on April 26, 2022)
8.1*	List of subsidiaries of the Registrant

Exhibit Number	Description of Document
11.1	Code of Business Conduct and Ethics of the Registrant (incorporated by reference to Exhibit 99.1 from our registration statement on Form F-1 (File No. 333-252210), as amended, initially filed publicly with the SEC on January 19, 2021)
12.1*	Certification by Principal Executive Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
12.2*	Certification by Principal Accounting Officer Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
13.1**	Certification by Principal Executive Officer Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
13.2**	Certification by Principal Accounting Officer Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
15.1*	Consent of Jingtian & Gongcheng
15.2*	Consent of Walkers (Hong Kong)
15.3*	Consent of Greenberg Traurig
15.4*	Consent of PricewaterhouseCoopers Zhong Tian LLP, Independent Registered Public Accounting Firm
15.5*	Submission under Item 16I(a) of Form 20-F in relation to the Holding Foreign Companies Accountable Act
101.INS*	XBRL Instance Document
101.SCH*	XBRL Taxonomy Extension Schema Document
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	XBRL Taxonomy Extension Presentation Linkbase Document
104*	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)

* Filed herewith
** Furnished herewith
† Portions of this exhibit have been omitted in accordance with Item 601(b)(10)(iv) of Regulation S-K.
# Certain of the appendices, annexes, exhibits and/or schedules to this exhibit have been omitted in accordance with Regulation S-K Item 601(b)(2). The Registrant agrees to furnish supplementally a copy of all omitted exhibits and schedules to the SEC upon its request.

SIGNATURES

The registrant hereby certifies that it meets all of the requirements for filing its annual report on Form 20-F and that it has duly caused and authorized the undersigned to sign this annual report on its behalf.
Date: April 28, 2023

Adagene Inc.

By: /s/ PETER LUO
Name: Peter Luo
Title: *Chief Executive Officer*

ADAGENE INC.

INDEX TO THE CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Adagene Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Adagene Inc. and its subsidiaries (the "Company") as of December 31, 2022 and 2021, and the related consolidated statements of comprehensive loss, of changes in shareholders' equity (deficit) and of cash flows for each of the three years in the period ended December 31, 2022, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022 in conformity with accounting principles generally accepted in the United States of America.

Change in Accounting Principle

As discussed in Note 2 to the consolidated financial statements, the Company changed the manner in which it accounts for leases in 2022.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers Zhong Tian LLP

Shanghai, the People's Republic of China
April 28, 2023

We have served as the Company's auditor since 2020.

ADAGENE INC.

CONSOLIDATED BALANCE SHEETS

AS OF DECEMBER 31, 2021 AND 2022

	Notes	As of December 31, 2021 US$	As of December 31, 2022 US$
ASSETS			
Current assets:			
Cash and cash equivalents		174,391,243	143,758,678
Accounts receivable, net	3,10	3,000,000	—
Amounts due from related parties	13	4,506,670	619,432
Prepayments and other current assets	4	4,055,921	4,937,323
Total current assets		**185,953,834**	**149,315,433**
Property, equipment and software, net	5	3,487,617	2,782,963
Operating lease right-of-use assets	14	—	191,877
Other non-current assets		69,275	109,572
TOTAL ASSETS		**189,510,726**	**152,399,845**
LIABILITIES AND SHAREHOLDERS' EQUITY			
Current liabilities:			
Accounts payable		3,321,615	3,666,124
Contract liabilities		5,500,000	15,107,276
Amounts due to related parties	13	10,466,061	19,323,337
Accruals and other current liabilities	6	4,379,243	3,212,809
Income tax payable	11	1,657,450	—
Short-term borrowings	7	3,121,226	10,768,745
Current portion of long-term borrowings	7	1,376,319	2,850,128
Current portion of operating lease liabilities	14	—	151,983
Total current liabilities		**29,821,914**	**55,080,402**
Long-term borrowings	7	2,991,829	14,146,541
Operating lease liabilities	14	—	53,834
Deferred tax liabilities	11	44,163	—
Other non-current liabilities		94,107	28,718
TOTAL LIABILITIES		**32,952,013**	**69,309,495**
Commitments and contingencies	15		
Shareholders' equity:			
Ordinary shares (par value of US$0.0001 per share; 640,000,000 shares authorized, and 54,595,667 shares issued and outstanding as of December 31, 2021; and 640,000,000 shares authorized, 54,065,709 shares issued and outstanding as of December 31, 2022)		5,627	5,497
Treasury shares, at cost (94,074 shares as of December 31, 2021 and1 share as of as of December 31, 2022)	17	(619,605)	(4)
Additional paid-in capital		336,099,931	342,739,268
Accumulated other comprehensive loss		(93,981)	(849,305)
Accumulated deficit		(178,833,259)	(258,805,106)
Total shareholders' equity		**156,558,713**	**83,090,350**
TOTAL LIABILITIES AND SHAREHOLDERS' EQUITY		**189,510,726**	**152,399,845**

The accompanying notes are an integral part of these consolidated financial statements.

ADAGENE INC.

CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS

FOR THE YEARS ENDED DECEMBER 31, 2020, 2021 AND 2022

	Notes	For the years ended December 31, 2020	2021	2022
		US$	US$	US$
Revenue				
Licensing and collaboration revenue	10	700,913	10,175,258	9,292,724
Expenses				
Research and development expenses		(33,538,035)	(68,099,385)	(81,339,540)
Third parties		(23,645,740)	(55,020,367)	(46,212,077)
Related parties		(9,892,295)	(13,079,018)	(35,127,463)
Administrative expenses		(10,314,536)	(14,439,962)	(11,873,867)
Loss from operations		**(43,151,658)**	**(72,364,089)**	**(83,920,683)**
Interest income		629,288	76,166	377,501
Interest expense		(202,165)	(363,762)	(693,323)
Other income, net		971,949	1,778,822	2,168,388
Foreign exchange gain (loss), net		(644,693)	(603,459)	2,555,325
Loss before income tax		**(42,397,279)**	**(71,476,322)**	**(79,512,792)**
Income tax expense	11	—	(1,701,613)	(459,055)
Net loss attributable to Adagene Inc.'s shareholders		**(42,397,279)**	**(73,177,935)**	**(79,971,847)**
Other comprehensive income (loss)				
Foreign currency translation adjustments, net of nil tax		(6,087)	257,000	(755,324)
Total comprehensive loss attributable to Adagene Inc.'s shareholders		**(42,403,366)**	**(72,920,935)**	**(80,727,171)**
Net loss attributable to Adagene Inc.'s shareholders		**(42,397,279)**	**(73,177,935)**	**(79,971,847)**
Accretion of convertible redeemable preferred shares to redemption value	8	(248,113)	(28,553)	—
Net loss attributable to ordinary shareholders		**(42,645,392)**	**(73,206,488)**	**(79,971,847)**
Weighted average number of ordinary shares used in per share calculation:				
—Basic	12	15,950,698	50,032,009	54,135,084
—Diluted	12	15,950,698	50,032,009	54,135,084
Net loss per ordinary share				
—Basic	12	(2.67)	(1.46)	(1.48)
—Diluted	12	(2.67)	(1.46)	(1.48)

The accompanying notes are an integral part of these consolidated financial statements.

ADAGENE INC.

CONSOLIDATED STATEMENTS OF CHANGES IN SHAREHOLDERS' EQUITY (DEFICIT)

FOR THE YEARS ENDED DECEMBER 31, 2020, 2021 AND 2022

	Ordinary shares		Treasury shares		Subscriptions receivable from shareholders	Additional paid-in capital	Accumulated other comprehensive loss	Accumulated deficit	Total shareholders' equity (deficit)
	Number of shares	Amount	Number of shares	Amount					
		US$		US$	US$	US$	US$	US$	US$
Balance as of January 1, 2020	**15,193,136**	**1,519**	**—**	**—**	**(197,068)**	**6,789,542**	**(344,894)**	**(63,258,045)**	**(57,008,946)**
Net loss	—	—	—	—	—	—	—	(42,397,279)	(42,397,279)
Other comprehensive income (loss)	—	—	—	—	—	—	(6,087)	—	(6,087)
Exercise of share options (Note 9)	3,694,934	370	—	—	(6,975,124)	7,115,682	—	—	140,928
Share-based compensation	—	—	—	—	—	10,129,541	—	—	10,129,541
Accretion of convertible redeemable preferred shares to redemption value	—	—	—	—	—	(248,113)	—	—	(248,113)
Balance as of December 31, 2020	**18,888,070**	**1,889**	**—**	**—**	**(7,172,192)**	**23,786,652**	**(350,981)**	**(105,655,324)**	**(89,389,956)**
Net loss	—	—	—	—	—	—	—	(73,177,935)	(73,177,935)
Other comprehensive income	—	—	—	—	—	—	257,000	—	257,000
Exercise of share options (Note 9)	233,957	23	—	—	—	226,758	—	—	226,781
Issuance of ordinary shares under performance incentive plan (Note 9)	23,734	2	—	—	—	416,749	—	—	416,751
Subscription from shareholders	—	—	—	—	381,282	—	—	—	381,282
Share-based compensation	—	—	—	—	—	18,679,658	—	—	18,679,658
Accretion of convertible redeemable preferred shares to redemption value	—	—	—	—	—	(28,553)	—	—	(28,553)
Conversion of convertible redeemable preferred shares to ordinary shares upon the completion of initial public offering ("IPO")	27,249,824	2,725	—	—	—	154,475,235	—	—	154,477,960
Issuance of ordinary shares upon IPO, net of issuance cost	10,571,375	1,057	—	—	—	147,094,280	—	—	147,095,337
Purchase of treasury shares under share repurchase program (Note 17)	—	—	(295,174)	(2,361,576)	—	—	—	—	(2,361,576)
Retirement of treasury shares (Note 17)	(201,100)	(20)	201,100	1,741,971	—	(1,750,041)	—	—	(8,090)
Surrender of ordinary shares for repayment of promissory notes (Note 9)	(491,119)	(49)	—	—	6,790,910	(6,800,807)	—	—	(9,946)
Balance as of December 31, 2021	**56,274,741**	**5,627**	**(94,074)**	**(619,605)**	**—**	**336,099,931**	**(93,981)**	**(178,833,259)**	**156,558,713**
Net loss	—	—	—	—	—	—	—	(79,971,847)	(79,971,847)
Other comprehensive income (loss)	—	—	—	—	—	—	(755,324)	—	(755,324)
Exercise of share options (Note 9)	197,975	20	—	—	—	323,192	—	—	323,212
Issuance of ordinary shares under performance incentive plan (Note 9)	99,999	10	—	—	—	391,985	—	—	391,995
Share-based compensation	—	—	—	—	—	10,520,282	—	—	10,520,282
Purchase of treasury shares under share repurchase program (Note 17)	—	—	(1,512,932)	(3,976,681)	—	—	—	—	(3,976,681)
Retirement of treasury shares (Note 17)	(1,607,005)	(160)	1,607,005	4,596,282	—	(4,596,122)	—	—	—
Balance as of December 31, 2022	**54,965,710**	**5,497**	**(1)**	**(4)**	**—**	**342,739,268**	**(849,305)**	**(258,805,106)**	**83,090,350**

The accompanying notes are an integral part of these consolidated financial statements.

ADAGENE INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

FOR THE YEARS ENDED DECEMBER 31, 2020, 2021 AND 2022

	For the years ended December 31,		
	2020	**2021**	**2022**
	US$	**US$**	**US$**
Cash flows from operating activities:			
Net loss	(42,397,279)	(73,177,935)	(79,971,847)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	858,408	1,125,032	1,145,995
Net loss on disposal of property, equipment, software and operating lease right-of-use asset	327	18,973	6,811
Share-based compensation	10,129,541	18,679,658	10,520,282
Interest income on promissory notes	—	(9,946)	—
Amortization of right-of use assets and interest of lease liabilities	—	—	303,535
Foreign exchange loss (gain), net	644,693	603,459	(2,555,325)
Changes in operating assets and liabilities:			
Accounts receivable, net	480,000	(3,000,000)	3,000,000
Prepayments and other current assets	(2,337,011)	(231,287)	(881,402)
Amount due from related parties	1,300,790	(4,374,274)	3,887,238
Other non-current assets	(13,292)	(24,210)	(40,297)
Accounts payable	1,097,261	1,511,640	344,509
Contract liabilities	(267,842)	4,774,464	9,607,276
Amount due to related parties	639,579	7,930,703	8,857,276
Accruals and other current liabilities	1,243,150	1,057,491	(823,928)
Lease liabilities	—	—	(280,465)
Income tax payable	—	1,657,450	(1,657,450)
Deferred tax liabilities	—	44,163	(44,163)
Other non-current liabilities	91,955	—	(29,732)
Net cash used in operating activities	**(28,529,720)**	**(43,414,619)**	**(48,611,687)**
Cash flows from investing activities:			
Withdrawal of short-term investments	8,000,000	—	—
Proceeds from disposal of property, equipment and software	7,930	—	4,892
Purchase of property, equipment and software	(935,199)	(2,509,926)	(690,938)
Net cash generated from (used in) investing activities	**7,072,731**	**(2,509,926)**	**(686,046)**
Cash flows from financing activities:			
Proceeds from borrowings	6,083,650	4,386,860	25,830,030
Proceeds from share subscriptions	—	381,282	—
Proceeds from exercise of share options	140,928	231,521	323,212
Proceeds from initial public offering, net of underwriting commissions	—	149,411,950	—
Repayment of borrowings	(1,063,670)	(5,089,717)	(4,353,588)
Payment of initial public offering costs	(721,532)	(1,595,088)	—
Purchase of treasury shares under stock repurchase program	—	(2,361,576)	(3,976,681)
Costs for retirement of treasury shares	—	(8,090)	—
Net cash generated from financing activities	**4,439,376**	**145,357,142**	**17,822,973**
Effect of exchange rate on cash and cash equivalents	(364,177)	(192,352)	842,195
Net increase (decrease) in cash and cash equivalents	**(17,381,790)**	**99,240,245**	**(30,632,565)**
Cash and cash equivalents at the beginning of year	92,532,788	75,150,998	174,391,243
Cash and cash equivalents at the end of year	**75,150,998**	**174,391,243**	**143,758,678**
Supplemental cash flow disclosures:			
Interest paid	202,165	359,569	603,680
Income tax paid	—	—	2,433,241
Cash paid for fixed operating lease costs included in the measurement of lease obligations in operating activities	—	—	313,929
Right-of-use assets obtained in exchange for operating lease obligations	—	—	217,227
Non-cash activities:			
Accretion of convertible redeemable preferred shares to redemption value	248,113	28,553	—
Conversion of preferred shares	—	154,477,960	—
Payables for deferred initial public offering cost	2,276,183	—	—
Retirement of treasury shares	—	1,741,971	4,596,282
Surrender of ordinary shares for repayment of promissory notes	—	6,800,856	—

The accompanying notes are an integral part of these consolidated financial statements.

ADAGENE INC.

NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS

DECEMBER 31, 2020, 2021 AND 2022

1. ORGANIZATION AND BASIS OF PRESENTATION

Adagene Inc. (the "Company") is a limited liability company incorporated in the Cayman Islands on February 25, 2011. The Company, together with its subsidiaries (collectively, the "Group"), are principally engaged in research, development and production of monoclonal antibody drugs for cancers.

On February 8, 2021, the Company's registration statement relating to its initial public offering ("IPO") of its American Depositary Shares ("ADSs") was declared effective by the Securities and Exchange Commission ("SEC") and the shares of its ADSs began trading on the NASDAQ Global Market on February 9, 2021. The public offering price of the ADSs sold in the IPO was $19.00 per ADS. The IPO closed on February 11, 2021, pursuant to which the Company issued 8,457,100 ADSs, including the exercise in full of the underwriters' option to purchase 1,103,100 additional ADSs from the Company. The Company received net proceeds of approximately $145.9 million, after underwriting discounts, commissions and estimated offering expenses. Each ADS represents one and one quarter (1.25) ordinary shares of the Company. Upon the completion of the IPO, all outstanding shares of the convertible redeemable preferred shares were converted into ordinary shares.

As of December 31, 2022, the Company's principal subsidiaries are as follows:

Entity	Date of incorporation	Place of incorporation	Percentage of legal ownership by the Company		Principal activities
Adagene (Hong Kong) Limited	December 12, 2011	Hong Kong	100	%	Investment holding
Adagene Incorporated	September 20, 2017	The United States of America	100	%	Research and development of innovative medicines
Adagene (Suzhou) Limited	February 28, 2012	The People's Republic of China ("PRC" or "China")	100	%	Research and development of innovative medicines
Adagene Australia PTY Ltd.	May 30, 2018	Australia	100	%	Research and development of innovative medicines
Adagene PTE. Ltd.	March 27, 2020	Singapore	100	%	Research and development of innovative medicines
Adagene AG	August 31, 2020	Switzerland	100	%	Research and development of innovative medicines
Adagene Project C1 PTE. Ltd.	March 25, 2022	Singapore	100	%	Research and development of innovative medicines

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of presentation

The accompanying consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles ("U.S. GAAP"). References to specific U.S. GAAP principles throughout these notes to the accompanying financial statements are to the Accounting Standards Codification ("ASC"), as published by the U.S. Financial Accounting Standards Board ("FASB").

Principles of Consolidation

The consolidated financial statements of the Group include the financial statements of the Company and its subsidiaries. All significant intercompany balances and transactions have been eliminated upon consolidation.

Use of estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosures of contingent assets and liabilities at the balance sheet dates and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in the Group's consolidated financial statements include, but are not limited to, licensing and collaboration revenue recognition, research and development expense allocation, the useful lives and impairment of long-lived assets, tax valuation allowance, share-based compensation expenses, and measurement of right-of-use assets and lease liabilities. Management bases the estimates on historical experience and various other assumptions that are believed to be reasonable, the results of which form the basis for making judgments about the carrying values of assets and liabilities. Actual results could materially differ from those estimates.

Foreign currency translation

The functional currency of the Company, Adagene (Hong Kong) Limited, Adagene Incorporated, Adagene PTE. Ltd. and Adagene Project C1 PTE. Ltd. is the United States dollar ("US$"). The functional currency of the Company's PRC subsidiary is Renminbi ("RMB"). The functional currency of the Company's Australian subsidiary is Australian dollar ("AU$"). The functional currency of the Company's Swiss subsidiary is Swiss Franc ("CHF"). The determination of the respective functional currency is based on the criteria stated in ASC 830, *Foreign Currency Matters*. The Company uses US$ as its reporting currency. The financial statements of the Company's PRC, Australian and Swiss subsidiaries are translated from the functional currency to the reporting currency.

Transactions denominated in foreign currencies are remeasured into the functional currency at the exchange rates quoted by the People's Bank of China (the "PBOC") prevailing on the transaction dates. Monetary assets and liabilities denominated in foreign currencies are re-measured at the exchange rates prevailing at the balance sheet date. Non-monetary items that are measured in terms of historical costs in foreign currency are re-measured using the exchange rates at the dates of the initial transactions. Exchange gains and losses are included in the consolidated statements of comprehensive loss.

Assets and liabilities are translated at the exchange rates at the balance sheet date, equity accounts are translated at historical exchange rates and revenues, expenses, gains and losses are translated using the average rate for the year. Translation adjustments are reported as accumulated comprehensive loss and are shown as a separate component of other comprehensive loss in the consolidated statements of comprehensive loss.

Cash and cash equivalents

Cash and cash equivalents primarily consist of cash and demand deposits which are highly liquid. The Group considers highly liquid investments that are readily convertible to known amounts of cash and with original maturities from the date of purchase of three months or less to be cash equivalents. All cash and cash equivalents are unrestricted as to withdrawal and use.

Accounts receivable and allowance for doubtful accounts

Account receivable is recorded when the Group has an unconditional right to consideration. A right to consideration is unconditional if only the passage of time is required before payment of that consideration is due. Accounts receivable is carried at net realizable value. An allowance for doubtful accounts is recorded in the period when collection of the amount is no longer probable. In evaluating the collectability of receivable balances, the Group considers specific evidence including the aging of the receivable, the customer's payment history, its current credit-worthiness and other factors. Accounts receivable is written off when management determines a balance is uncollectable after all collection efforts have ceased.

Fair value measurements

The Group applies ASC 820, *Fair Value Measurements and Disclosures*. ASC 820 defines fair value, establishes a framework for measuring fair value and expands disclosures about fair value measurements. ASC 820 requires disclosures to be provided for fair value measurements. ASC 820 establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value as follows:

Level 1—Observable inputs that reflect quoted prices (unadjusted) for identical assets or liabilities in active markets.

Level 2—Other inputs that are directly or indirectly observable in the marketplace.

Level 3—Unobservable inputs which are supported by little or no market activity.

ASC 820 describes three main approaches to measuring the fair value of assets and liabilities: (1) market approach; (2) income approach; and (3) cost approach. The market approach uses prices and other relevant information generated from market transactions involving identical or comparable assets or liabilities. The income approach uses valuation techniques to convert future amounts to a single present value amount. The measurement is based on the value indicated by current market expectations about those future amounts. The cost approach is based on the amount that would currently be required to replace an asset.

The carrying amounts of cash and cash equivalent, accounts receivable, amounts due to related parties and other current assets, accounts payable, amounts due to related parties, accrued liabilities and other current liabilities and short-term borrowings approximate their fair values because of their generally short maturities. The carrying amount of long-term borrowings approximate their fair values since they bear interest rates which approximate market interest rates.

The Group did not transfer any assets or liabilities in or out of Level 3 during the years ended December 31, 2021 or 2022.

The Group had no financial assets and liabilities measured and recorded at fair value on a nonrecurring basis as of December 31, 2021 and 2022.

Property, equipment and software

Property and equipment and software are stated at cost less accumulated depreciation and amortization. Depreciation and amortization are computed using the straight-line method over the estimated useful lives of the assets as follows:

Category	Estimated Useful Life
Machinery and laboratory equipment	5 years
Vehicles	4 years
Furniture and tools	3 - 5 years
Electronic equipment	3 years
Computer software	3 - 5 years
Leasehold improvements	Lesser of lease terms or estimated useful lives of the assets

Repair and maintenance costs are charged to expense as incurred, whereas the cost of renewals and betterments that extend the useful lives of property, equipment and software are capitalized as additions to the related assets. Retirements, sales and disposals of assets are recorded by removing the cost and accumulated depreciation and amortization from the asset and accumulated depreciation and amortization accounts with any resulting gain or loss reflected in the consolidated statements of comprehensive loss.

Impairment of long-lived assets

The Group evaluates the recoverability of its long-lived assets, including fixed assets and intangible assets with finite lives, for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be fully recoverable. When these events occur, the Group measures impairment by comparing the carrying amount of the assets to the estimated undiscounted future cash flows expected to result from the use of the assets and their eventual disposition. If the sum of the expected undiscounted cash flows is less than the carrying amount of the assets, the Group recognizes an impairment loss based on the excess of the carrying amount of the assets over their fair value. Fair value is generally determined by discounting the cash flows expected to be generated by the assets, when the market prices are not readily available. The adjusted carrying amount of the assets is the new cost basis and is depreciated over the assets' remaining useful lives. Long-lived assets are grouped with other assets and liabilities at the lowest level for which identifiable cash flows are largely independent of the cash flows of other assets and liabilities.

No impairment loss was recorded for the years ended December 31, 2020, 2021 and 2022.

Segment reporting

In accordance with ASC 280, *Segment Reporting*, the Group's chief operating decision maker ("CODM") has been identified as the Chief Executive Officer. The Group's CODM reviews the consolidated results of operations when making decisions about allocating resources and assessing performance of the Group. The Group operates and manages it business as a single segment. No geographical segments are presented as a substantial portion of the Group's long-lived assets are located in the PRC with the exception of certain laboratory and electronic equipment which are located in the U.S.

Revenue recognition

At contract inception of collaboration and out-licensing arrangements, the Group analyzes its arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements* ("ASC 808") to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, the Group first determines which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are reflective of a vendor-customer relationship and therefore within the scope of ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently. Under the criteria of ASC 606, the Group recognizes revenue to depict the transfer of control of promised goods or services to customers in an amount that reflects the consideration to which the entity expects to receive in exchange for those goods or services.

The Group adopted ASC 606 for all periods presented. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Group only applies the five-step model to contracts when it is probable that the entity will collect substantially all the consideration to which it is entitled in exchange for the goods or services it transfers to the customer. The Group reviews the contract to determine which performance obligations are distinct and represent a promise to provide distinct goods or services or a series of distinct goods or services as defined by the standard. The Group recognizes as revenue the amount of the transaction price that is allocated to each performance obligation as and when that performance obligation is satisfied.

Licenses of Intellectual Property: Upfront non-refundable payments for licensing the Group's intellectual property are evaluated to determine if the license is distinct from the other performance obligations identified in the arrangement. For licenses determined to be distinct, the Group recognizes revenues from non-refundable, up-front fees allocated to the license at a point in time, when the transfer of control of the license to the licensee occurs and the licensee is able to use and benefit from the license. For licenses determined not to be distinct, the Group accounts for the promise to grant a license and those other promised goods or services together as a single performance obligation when recognizing revenue.

Research and Development Services: The portion of a transaction price allocated to research and development services performance obligations is deferred and recognized as collaboration revenue over time as delivery or performance of such services occurs.

Milestone Payments: At the inception of each arrangement that includes development, commercialization, and regulatory milestone payments, the Group evaluates whether the milestones are considered probable of being reached and to the extent that a significant reversal of cumulative revenue would not occur in future periods, estimates the amount to be included in the transaction price using the most likely amount method. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which the Group recognizes revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, the Group re-evaluates the probability of achieving such development milestones and any related constraint, and if necessary, adjust the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Group recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Contract assets and contract liabilities

When a customer pays consideration before the Group transfers products or services, the Group records its obligation as a contract liability; When the Group satisfies its performance obligations by providing products or services to a customer before the customer pays consideration and before payment is due, the Group recognizes its rights to consideration as a contract asset.

Research and development expenses

Elements of research and development expenses primarily include (1) payroll and other related costs of personnel engaged in research and development activities, (2) costs related to pre-clinical testing of the Group's technologies under development and clinical trials such as payments to contract research organizations ("CRO") and contract manufacturing organizations ("CMO"), investigators and clinical trial sites that conduct the clinical studies; (3) costs to develop the product candidates, including raw materials and supplies, product testing, depreciation and amortization, and facility related expenses, and (4) other research and development expenses. Research and development costs are expensed as incurred when the related research and development services are provided to the Group and the resulting assets, if any, have no alternative future uses. As of December 31, 2021 and 2022, the Group had several ongoing clinical studies in various clinical trial stages. The contracts with CRO and CMO are generally cancellable, with notice, at the Group's option. The Group did not record any accrued expenses related to cancellation of CRO or CMO contracts as of December 31, 2021 or 2022 as the Group did not have any plan to cancel the existing CRO or CMO contracts.

Government subsidies

Government subsidies primarily consist of financial subsidies received from provincial and local governments for operating a business in their jurisdictions and compliance with specific policies promoted by the governments. The Group's PRC based subsidiary received government subsidies from certain local government. The Group's government subsidies consist of specific subsidies and other subsidies. Specific subsidies are subsidies that the local government has set certain conditions for the subsidies. Other subsidies are the subsidies that the local government has not set any conditions and are not tied to future trends or performance of the Group, receipt of such subsidy income is not contingent upon any further actions or performance of the Group and the amounts do not have to be refunded under any circumstances. These specific subsidies are recorded as other non-current liabilities upon receipt and are recognized as other income when the conditions are met. Other subsidies are recognized as other income upon receipt as further performance by the Group is not required. In addition, the Group's Australian subsidiary received research and development tax incentive from the Australian Taxation Office. The tax incentive was recognized as other income upon receipt as the incentive was not dependent upon having a tax liability and further performance by the Group was not required.

Government subsidies of US$0.8 million, US$1.4 million and US$2.1 million were received and recognized as other income during the years ended December 31, 2020, 2021 and 2022, respectively.

Leases

Prior to the adoption of ASC 842, *Leases* ("ASC 842") on January 1, 2022:

Leases, mainly leases of office spaces where substantially all the rewards and risks of ownership of assets remain with the lessor are accounted for as operating leases. Payments made under operating leases are recognized as an expense on a straight-line basis over the lease term. The Group had no capital leases for any of the years stated herein.

Upon and hereafter the adoption of ASC 842 on January 1, 2022:

The Group determines if an arrangement is or contains a lease at inception. For arrangements that meet the definition of a lease, the Group determines the classification of the lease based on the relevant factors present and records a right-of-use ("ROU") asset and lease liability at the lease commencement date. ROU assets represent the right to use an underlying asset for the lease term and lease liabilities represent the obligation to make lease payments arising from the lease. ROU assets and lease liabilities are calculated as the present value of the lease payments not yet paid. As the rate implicit in the Group's leases is not typically readily available, the Group uses an incremental borrowing rate based on the information available at the lease commencement date in determining the present value of lease payments. This incremental borrowing rate reflects the fixed rate at which the Group could borrow the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. ROU assets include any lease prepayments and are reduced by lease incentives. Operating lease expense for lease payments is recognized on a straight-line basis over the lease term. Lease terms are based on the non-cancelable term of the lease and may contain options to extend the lease when it is reasonably certain that the Group will exercise that option.

Operating leases are included in operating lease right-of-use assets and lease liabilities on the consolidated balance sheet. Lease liabilities that become due within one year of the balance sheet date are classified as current liabilities.

The Group has elected to adopt the following lease policies in conjunction with the adoption of ASU 2016-02: (i) elect for each lease not to separate non-lease components from lease components and instead to account for each separate lease component and the non-lease components associated with that lease component as a single lease component; (ii) for leases that have lease terms of 12 months or less and does not include a purchase option that is reasonably certain to exercise, the Group elected not to apply ASC 842 recognition requirements; and (iii) the Group elected to apply the package of practical expedients for existing arrangements entered into prior to January 1, 2022 to not reassess (a) whether an arrangement is or contains a lease, (b) the lease classification.

In connection with the adoption of ASC 842 on January 1, 2022, the Group recorded an impact of approximately US$0.6 million and US$0.6 million for the recognition of operating lease right-of-use-assets and operating lease liabilities, respectively, on its consolidated balance sheet, which are primarily related to the lease of the Group's offices. The adoption of ASC 842 did not have a material impact on the Group's consolidated statements of comprehensive loss and cash flows.

Comprehensive income (loss)

Comprehensive income (loss) is defined as the changes in equity of the Group during a period from transactions and other events and circumstances excluding transactions resulting from investments by shareholders and distributions to shareholders. Accumulated other comprehensive income (loss) of the Group includes foreign currency translation adjustments related to the Group and its subsidiaries whose functional currency is not US$.

Income taxes

The Group follows the liability method of accounting for income taxes in accordance with ASC 740, *Income Taxes* ("ASC 740"). Under this method, deferred tax assets and liabilities are determined based on the difference between the financial reporting and tax bases of assets and liabilities using enacted tax rates that will be in effect in the period in which the differences are expected to reverse. The Group records a valuation allowance to offset deferred tax assets if based on the weight of available evidence, it is more likely than not that some portion, or all, of the deferred tax assets will not be realized. The effect on deferred taxes of a change in tax rate is recognized in tax expense in the period that includes the enactment date of the change in tax rate.

The Group evaluates its uncertain tax positions using the provisions of ASC 740, which prescribes a recognition threshold that a tax position is required to meet before being recognized in the consolidated financial statements.

The Group recognizes in the consolidated financial statements the benefit of a tax position which is "more likely than not" to be sustained under examination based solely on the technical merits of the position assuming a review by tax authorities having all relevant information. Tax positions that meet the recognition threshold are measured using a cumulative probability approach, at the largest amount of tax benefit that has a greater than fifty percent likelihood of being realized upon settlement. It is the Group's policy to recognize interest and penalties related to unrecognized tax benefits, if any, as a component of income tax expense.

Borrowings

Borrowings are recognized initially at fair value, net of transaction costs incurred. Borrowings are subsequently stated at amortized cost; any difference between the proceeds (net of transaction costs) and the redemption value is recognized in the consolidated statements of comprehensive loss over the period of the borrowings using the effective interest method.

Share-based compensation

The Company grants restricted shares and stock options to eligible employees and nonemployees and accounts for share-based compensation in accordance with ASC 718, Compensation-Stock Compensation.

Share-based compensation awards are measured at the grant date fair value of the awards and recognized as expenses (a) immediately at the grant date if no vesting conditions are required; (b) for share-based awards granted with only service conditions, using the straight-line method over the vesting period; or (c) for share-based awards granted with service conditions and performance conditions, using the graded vesting method over the vesting period if and when the Company concludes that it is probable that the performance conditions will be achieved.

A change in any of the terms or conditions of share-based awards is accounted for as a modification of the awards. The Group calculates incremental compensation expense of a modification as the excess of the fair value of the modified awards over the fair value of the original awards immediately before its terms are modified at the modification date. For vested awards, the Group recognizes incremental compensation cost in the period when the modification occurs. For awards not being fully vested, the Group recognizes the sum of the incremental compensation expense and the remaining unrecognized compensation expense for the original awards over the remaining requisite service period after modification.

Net loss per share

In accordance with ASC 260, *Earnings Per Share*, basic net loss per share is computed by dividing net loss attributable to ordinary shareholders by the weighted average number of unrestricted ordinary shares outstanding during the year using the two-class method. Under the two-class method, net loss is allocated between ordinary shares and other participating securities based on dividends declared (or accumulated) and participating rights in undistributed earnings as if all the earnings for the reporting period had been distributed. Diluted net loss per share is calculated by dividing net loss attributable to ordinary shareholders, as adjusted for the effect of dilutive ordinary equivalent shares, if any, by the weighted average number of ordinary and dilutive ordinary equivalent shares outstanding during the period. Ordinary equivalent shares include ordinary shares issuable upon the exercise of share options, using the treasury stock method. Ordinary share equivalents are excluded from the computation of diluted earnings per share if their effects are anti-dilutive. For the periods presented herein, the computation of basic net loss per share using the two-class method is not applicable as the Group is in a net loss position and the participating securities do not have contractual rights and obligations to share in the losses of the Group.

Employee defined contribution plan

As stipulated by the regulations of the PRC, full-time employees of the Group are entitled to staff welfare benefits including medical care, welfare subsidies, unemployment insurance and pension benefits through a PRC government-mandated multi-employer defined contribution plan. The Group is required to accrue for these benefits based on certain percentages of the qualified employees' salaries. The Group is required to make contributions to the plans out of the amounts accrued. The PRC government is responsible for the medical benefits and the pension liability to be paid to these employees and the Group's obligations are limited to the amounts contributed. The Group has no further payment obligations once the contributions have been paid. The Group recorded employee benefit expenses of US$622,377 , US$2,223,493 and US$2,984,251 for the years ended December 31, 2020 , 2021 and 2022, respectively.

Concentration of risks

Concentration of credit risk

As of December 31, 2021 and 2022, the amount of cash and cash equivalents of US$3,650,474 and US$8,617,157 respectively, were held at major financial institutions located in Mainland China, and US$170,740,769 and US$135,141,521,respectively, were deposited with major financial institutions located outside of Mainland China. Management believes that these financial institutions are of high credit quality and continually monitors the credit worthiness of these financial institutions.

Accounts receivable is typically unsecured and denominated in US$ and is derived from revenues earned from customers. The Group manages credit risk of accounts receivable through ongoing monitoring of the outstanding balances.

Concentration of suppliers

A significant portion of the Group's research and development services were purchased from one supplier group, who collectively accounted for 21.5%,18.5% and 34.1%of the Group's total research and development services purchases for the years ended December 31, 2020, 2021 and 2022, respectively.

Business and economic risk

The Group believes that changes in any of the following areas could have a material adverse effect on the Group's future consolidated financial position, results of operations or cash flows: changes in the overall demand for services; competitive pressures due to new entrants; advances and new trends in new technologies and industry standards; changes in certain strategic relationships; regulatory considerations and risks associated with the Group's ability to attract employees necessary to support its growth. The Group's operations could also be adversely affected by significant political, regulatory, economic and social uncertainties in the PRC.

Foreign currency exchange rate risk

A significant portion of the Group's businesses are transacted in RMB, which is not a freely convertible currency. On January 1, 1994, the PRC government abolished the dual rate system and introduced a single rate of exchange as quoted daily by the PBOC. However, the unification of the exchange rates does not imply that the RMB may be readily convertible into US$ or other foreign currencies. All foreign exchange transactions continue to take place either through the PBOC or other banks authorized to buy and sell foreign currencies at the exchange rates quoted by the PBOC. Approval of foreign currency payments by the PBOC or other institutions requires submitting a payment application form together with suppliers' invoices, shipping documents and signed contracts.

From July 21, 2005, the RMB is permitted to fluctuate within a narrow and managed band against a basket of certain foreign currencies. For U.S. dollar against RMB, there was depreciation of approximately 2.29% in the year ended December 31,2021 and appreciation of approximately 9.24% in the year ended December 31, 2022, respectively. It is difficult to predict how market forces or PRC or U.S. government policy may impact the exchange rate between the RMB and the U.S. dollar in the future.

The functional currency and the reporting currency of the Company are the US$. However, the Group incurs portions of our expenses, and derives revenues, in currencies other than US$, in particular, the RMB. Any significant fluctuation of the valuation of RMB may materially affect the Group's cash flows, expenses, losses and financial position, and the value of any dividends payable on the American Depositary Shares in US$.

Recently issued accounting pronouncements

The Group is an emerging growth company ("EGC") as defined by the Jumpstart Our Business Startups Act ("JOBS Act"). The JOBS Act provides that an EGC can take advantage of extended transition periods for complying with new or revised accounting standards. This allows an EGC to delay adoption of certain accounting standards until those standards would otherwise apply to private companies. The Group elected to take advantage of the extended transition periods. However, this election will not apply should the Group cease to be classified as an EGC.

In February 2016, the FASB issued ASU No. 2016-02 (“ASU 2016-02”), *Leases* (Topic 842), which modifies lease accounting for lessees to increase transparency and comparability by recording lease assets and liabilities for operating leases and disclosing key information about leasing arrangements. In July 2018, the FASB issued ASU No. 2018-10 (“ASU 2018-10”), *Codification Improvements to Topic 842, Leases*, which clarifies certain aspects of the guidance issued in ASU 2016-02; and ASU No. 2018-11 (“ASU 2018-11”), *Leases (Topic 842): Targeted Improvements*, which provides entities with an additional (and optional) transition method to adopt the new leases standard. Under this new transition method, an entity initially applies the new leases standard at the adoption date and recognizes a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption. Consequently, an entity’s reporting for the comparative periods presented in the financial statements in which it adopts the new leases standard will continue to be in accordance with current U.S. GAAP (Topic 840, *Leases*). Further, the FASB issued ASU No. 2020-05 (“ASU 2020-05”), *Revenue from Contracts with Customers (Topic 606) and Leases (Topic 842): Effective Dates for Certain Entities,* which extends the adoption date for certain entities. For the Group, the updated guidance is effective for fiscal years beginning after December 15, 2021 and interim periods within fiscal years beginning after December 15, 2022. Early adoption is permitted. The Group adopted the new guidance on January 1, 2022, using the alternative transition approach. For additional information, see Note 14, *Leases*.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments* (“ASU 2016-13”). ASU 2016-13 is intended to improve financial reporting by requiring timelier recording of credit losses on loans and other financial instruments held by financial institutions and other organizations. This ASU requires the measurement of all expected credit losses for financial assets held at the reporting date based on historical experience, current conditions, and reasonable and supportable forecasts. This ASU requires enhanced disclosures to help investors and other financial statement users better understand significant estimates and judgments used in estimating credit losses, as well as the credit quality and underwriting standards of the Group’s portfolio. These disclosures include qualitative and quantitative requirements that provide additional information about the amounts recorded in the financial statements. In November 2019, the FASB issued ASU 2019-10, which extends the adoption date for certain registrants. The amendments in ASU 2016-13 are effective for fiscal years beginning after December 15, 2022, including interim periods within fiscal years beginning after December 15, 2023. The Group does not plan to early adopt ASU 2016-13 and does not expect the adoption of ASU 2016-13 to have a material impact on the financial statements including the notes to the financial statements.

In December 2019, the FASB issued ASU 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes*. This update simplifies the accounting for income taxes as part of the FASB’s overall initiative to reduce complexity in accounting standards. The amendments include removal of certain exceptions to the general principles of ASC 740, *Income Taxes*, and simplification in several other areas such as accounting for a franchise tax (or similar tax) that is partially based on income. The update is effective in fiscal years beginning after December 15, 2021. Certain amendments in this update should be applied retrospectively or modified retrospectively, all other amendments should be applied prospectively. The Group adopted ASU 2019-12 in 2022 and the adoption of ASU 2019-12 did not have a material impact on the financial statements including the notes to the financial statements.

In August 2020, the FASB issued ASU 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity’s Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity’s Own Equity*, which simplifies the accounting for convertible instruments by removing certain separation models in Subtopic 470-20, *Debt—Debt with Conversion and Other Options*, for convertible instruments and also increases information transparency by making disclosure amendments. The standard is effective for private companies for fiscal years beginning after December 15, 2023, including interim periods within those fiscal years. Early adoption is permitted, but no earlier than fiscal years beginning after December 15, 2020, including interim periods within those fiscal years. The Group is currently evaluating the impact of this accounting standard update on its consolidated financial statements.

In March 2022, the FASB issued ASU 2022-02, *Financial Instruments-Credit Losses (Topic 326): Troubled Debt Restructurings (“TDR”) and Vintage Disclosures* (“ASU 2022-02”). ASU 2022-02 eliminates the TDR recognition and measurement guidance, enhance existing disclosure requirements and introduce new requirements related to certain modifications of receivables made to borrowers experiencing financial difficulty. For entities that have not yet adopted ASU 2016-13, the ASU is effective upon adoption of the amendments in ASU 2016-13. Early adoption is not permitted before an entity's adoption of ASU 2016-13. The Group has not adopted ASU 2016-13 and is currently in the process of evaluating the impact of adoption of this guidance on its consolidated financial statements.

3. ACCOUNTS RECEIVABLE, NET

	As of December 31,	
	2021	2022
	US$	US$
Accounts receivable	3,000,000	—
Allowance for doubtful accounts	—	—
	3,000,000	—

4. PREPAYMENTS AND OTHER CURRENT ASSETS

Prepayments and other current assets consisted of the following:

	As of December 31,	
	2021	2022
	US$	US$
Prepayments	1,562,177	1,161,910
Deposits (a)	1,873,843	2,970,421
Others	619,901	804,992
	4,055,921	4,937,323

Note (a): The deposits represented the amounts that the Group paid to its CRO vendors for various outsourced research and development programs according to the terms of respective CRO agreements. The Group expects to recover the deposits if the programs fail or the agreements are cancelled.

5. PROPERTY, EQUIPMENT AND SOFTWARE, NET

Property, equipment and software consisted of the following:

	As of December 31,	
	2021	2022
	US$	US$
Machinery and laboratory equipment	5,252,399	5,293,386
Leasehold improvements	1,152,743	1,055,271
Electronic equipment	1,863,956	1,863,963
Furniture and tools	81,467	29,684
Vehicles	87,680	80,266
Software	371,636	369,698
Total property, equipment and software	8,809,881	8,692,268
Less: accumulated depreciation and amortization	(5,322,264)	(5,909,305)
Net book value	3,487,617	2,782,963

Depreciation and amortization expenses recognized for the years ended December 31, 2020, 2021 and 2022 were US$858,408, US$1,125,032 and US$1,145,995 respectively.

6. ACCRUALS AND OTHER CURRENT LIABILITIES

Accrued liabilities and other current liabilities consisted of the following:

	As of December 31,	
	2021	2022
	US$	US$
Professional service fees	935,434	1,647,490
Payroll and related liabilities	3,229,794	1,104,365
Utility and maintenance	8,685	40,718
Other taxes and surcharge	62,270	349,039
Others	143,060	71,197
	4,379,243	3,212,809

7. BORROWINGS

	As of December 31,	
	2021	2022
	US$	US$
Current		
Short-term borrowings:		
Bank loans	3,121,226	10,768,745
Current portion of long-term borrowings	1,376,319	2,850,128
Total current borrowings	4,497,545	13,618,873
Non-Current		
Long-term borrowings:		
Bank loans	2,991,829	14,146,541
Total non-current borrowings	2,991,829	14,146,541
Total borrowings	**7,489,374**	**27,765,414**

Short-term borrowings

In June 2020, the Group borrowed a loan with the amount of RMB10,000,000 (equivalent to approximately US$1,532,591) from Agricultural Bank of China Limited for a term of one year at the interest rate of 4.2% per annum. The borrowing was repaid in June 2021.

In September 2020, the Group borrowed a loan with the amount of RMB5,000,000 (equivalent to approximately US$766,295) from Bank of Ningbo Co., Ltd. for a term of one year at the interest rate of 4.2% per annum. The borrowing was repaid in September 2021.

In November 2020, the Group borrowed a loan with the amount of RMB5,000,000 (equivalent to approximately US$770,962) from China Merchants Bank Co., Ltd. for a term of one year at the interest rate of 4.1% per annum. The borrowing was repaid in November 2021.

In November 2020, the Group borrowed another loan with the amount of RMB5,000,000 (equivalent to approximately US$770,962) from China Merchants Bank Co., Ltd. for a term of one year at the interest rate of 4.1% per annum. The borrowing was also repaid in November 2021.

In June 2021, the Group borrowed a loan with the amount of RMB9,900,000 (equivalent to approximately US$1,552,771) from Agricultural Bank of China Limited for a term of one year at the interest rate of 4.05% per annum. The borrowing was repaid in May 2022.

In August 2021, the Group borrowed another loan with the amount of RMB10,000,000 (equivalent to approximately US$1,568,455) from Agricultural Bank of China Limited for a term of one year at the interest rate of 4.05% per annum. The borrowing was repaid in August 2022.

In March 2022, the Group borrowed a loan with the amount of RMB9,900,000 (equivalent to approximately US$1,421,474) from China Merchants Bank Co., Ltd. for a term of one year at the interest rate of 3.90% per annum.

In April 2022, the Group borrowed another loan with the amount of RMB20,100,000 (equivalent to approximately US$2,886,024) from China Merchants Bank Co., Ltd. for a term of one year at the interest rate of 3.70% per annum.

In July 2022, the Group borrowed a loan with the amount of RMB20,000,000 (equivalent to approximately US$2,871,665) from Bank of Jiangsu Co., Ltd. for a term of one year at the interest rate of 3.70% per annum.

In December 2022, the Group borrowed another loan with the amount of RMB25,000,000 (equivalent to approximately US$3,589,582) from China Construction Bank Corporation for a term of one year at the interest rate of 3.65% per annum.

Long-term borrowings

In February 2019, the Group borrowed a loan with the amount of RMB7,500,000 (equivalent to approximately US$1,076,874) from Shanghai Pudong Development Bank Co., Ltd. for a term of three years at the interest rate of 5.46% per annum. The Group repaid RMB375,000 (equivalent to approximately US$53,844) in 2019, RMB1,250,000 (equivalent to approximately US$179,479) in 2020, RMB3,375,000 (equivalent to approximately US$484,594) in 2021 and RMB2,500,000 (equivalent to approximately US$358,958) in 2022. As of December 31, 2021, RMB2,500,000 (equivalent to approximately US$358,958) repayable within twelve months for this agreement was classified as “Current portion of long-term borrowing” on the consolidated balance sheets. The loan was fully repaid in February 2022.

In June 2019, the Group borrowed a loan with the amount of RMB6,000,000 (equivalent to approximately US$861,500) from Shanghai Pudong Development Bank Co., Ltd. for a term of three years at the interest rate of 5.23% per annum. The Group repaid RMB300,000 (equivalent to approximately US$43,075) in 2019, RMB1,000,000 (equivalent to approximately US$143,583) in 2020, RMB2,700,000 (equivalent to approximately US$387,675) in 2021, and RMB2,000,000 (equivalent to approximately US$287,167)in 2022. As of December 31, 2021, RMB2,000,000 (equivalent to approximately US$287,167) repayable within twelve months for this agreement was classified as “Current portion of long-term borrowing” on the consolidated balance sheets. The loan was fully repaid in June 2022.

In September 2020, the Group borrowed a loan with the amount of RMB16,500,000 (equivalent to approximately US$2,369,124) from Shanghai Pudong Development Bank Co., Ltd. for a term of three years at the interest rate of 4.27% per annum.The Group repaid RMB1,650,000 (equivalent to approximately US$236,912) in 2021 and RMB3,850,000 (equivalent to approximately US$552,796) in 2022. As of December 31, 2021 and 2022, RMB3,850,000 (equivalent to approximately US$552,796) and RMB 11,000,000 (equivalent to approximately US$1,579,416) repayable within twelve months for this agreement were classified as “Current portion of long-term borrowing” on the consolidated balance sheets, respectively.

In September 2021, the Group borrowed a loan with the amount of RMB8,500,000 (equivalent to approximately US$1,220,458) from Shanghai Pudong Development Bank Co., Ltd. for a term of three years at the interest rate of 4.05% per annum. The Group repaid RMB425,000 (equivalent to approximately US$61,023) in 2022. As of December 31, 2021 and 2022, RMB425,000 (equivalent to approximately US$61,023) and RMB850,000 (equivalent to approximately US$122,046) repayable within twelve months for this agreement were classified as “Current portion of long-term borrowing” on the consolidated balance sheets, respectively.

In May 2022, the Group borrowed a loan with the amount of RMB30,000,000 (equivalent to approximately US$4,307,498) from Agricultural Bank of China Limited for a term of three years at the interest rate of 4.00% per annum. As of December 31, 2022, RMB3,000,000 (equivalent to approximately US$430,750) repayable within twelve months for this agreement was classified as "Current portion of long-term borrowing" on the consolidated balance sheets.

Also in May 2022, the Group borrowed a loan with the amount of RMB20,000,000 (equivalent to approximately US$2,871,665) from Shanghai Pudong Development Bank Co., Ltd. for a term of three years at the interest rate of 4.00% per annum. The Group repaid RMB500,000 (equivalent to approximately US$71,792) in 2022. As of December 31, 2022, RMB1,500,000 (equivalent to approximately US$215,375) repayable within twelve months for this agreement was classified as "Current portion of long-term borrowing" on the consolidated balance sheets.

In August 2022, the Group borrowed a loan with the amount of RMB9,900,000 (equivalent to approximately US$1,421,474) from Agricultural Bank of China Limited for a term of three years at the interest rate of 4.00% per annum. As of December 31, 2022, RMB1,000,000 (equivalent to approximately US$143,583) repayable within twelve months for this agreement was classified as "Current portion of long-term borrowing" on the consolidated balance sheets.

Also in August 2022, the Group borrowed a loan with the amount of RMB20,000,000 (equivalent to approximately US$2,871,665) from Shanghai Pudong Development Bank Co., Ltd. for a term of three years at the interest rate of 4.00% per annum. As of December 31, 2022, RMB1,000,000 (equivalent to approximately US$143,583) repayable within twelve months for this agreement was classified as "Current portion of long-term borrowing" on the consolidated balance sheets.

In November 2022, the Group borrowed a loan with the amount of RMB9,900,000 (equivalent to approximately US$1,421,474) from Agricultural Bank of China Limited for a term of three years at the interest rate of 4.00% per annum. As of December 31, 2022, RMB1,000,000 (equivalent to approximately US$143,583) repayable within twelve months for this agreement was classified as "Current portion of long-term borrowing" on the consolidated balance sheets.

Also in November 2022, the Group borrowed a loan with the amount of RMB10,000,000 (equivalent to approximately US$1,435,833) from Shanghai Pudong Development Bank Co., Ltd. for a term of three years at the interest rate of 4.00% per annum. As of December 31, 2022, RMB500,000 (equivalent to approximately US$71,792) repayable within twelve months for this agreement was classified as "Current portion of long-term borrowing" on the consolidated balance sheets.

The proceeds from the loans were primarily used to pay for the Group’s research and development activities in China, including CMC costs of clinical and preclinical programs. As of December 31, 2021 and 2022, none of the Group’s borrowings were collateralized in the respective loan agreements.

Future maturities of short-term borrowings and long-term borrowings

Future principal maturities of short-term borrowings and long-term borrowings as of December 31, 2021 and 2022 were as follows:

	As of December 31,	
	2021	2022
	US$	US$
2022	4,497,545	—
2023	1,858,619	13,618,873
2024	1,133,210	4,124,429
2025	—	10,022,112
	7,489,374	27,765,414

8. CONVERTIBLE REDEEMABLE PREFERRED SHARES AND WARRANTS

In November 2011, the Company issued convertible notes (“Series Pre-A Convertible Notes”) to certain investors in the amount of 4,590,908. The notes carried a simple interest (non-compounding) of 6% per annum as set out in the note purchase agreement. All outstanding principal balance and accrued but unpaid interest of the notes should be automatically converted into the convertible redeemable preferred shares of the Company at a price no more than US$1 per share.

In November 2014, the Company issued 5,473,957 Series A-1 convertible redeemable preferred shares ("Series A-1 Preferred Shares") to certain investors upon conversion of the Company's Series Pre-A convertible notes at a conversion price of US$1 per share. Concurrently, the Company issued 2,370,414 Series A-2 convertible redeemable preferred shares ("Series A-2 Preferred Shares") to certain investors at US$1.27 per share for a total consideration of US$3,000,000. Series A-1 Preferred Shares and Series A-2 Preferred Shares are collectively referred to as the Series A Preferred Shares.

From January through June 2016, the Company issued 7,494,537 Series B convertible redeemable preferred shares ("Series B Preferred Shares") to certain investors at US$3.74 per share for a total consideration of US$27,999,995.

From February through May 2018, the Company issued 5,597,354 Series C-1 convertible redeemable preferred shares ("Series C-1 Preferred Shares") to certain investors at US$8.93 per share for a total consideration of US$50,000,033. Concurrently, in February 2018, the Company also issued warrants to two Series C-1 investors at nil consideration ("Series C-1 Warrants"). The Series C-1 Warrants allowed the holders to purchase Series C-2 Preferred Shares (defined below) at the exercise price of US$10.21 per share for a total consideration of up to US$7,500,000. Series C-1 Warrants were exercisable, in whole or in part, at any time from the warrant issuance date to the earlier of i) April 1, 2019, ii) a deemed liquidation event or iii) the closing of the Qualified IPO. Series C-1 Warrants expired on April 1, 2019.

From June through November 2019, the Company issued 1,861,121 Series C-2 convertible redeemable preferred shares ("Series C-2 Preferred Shares") to certain investors at US$10.21 per share for a total consideration of US$18,999,999.

In December 2019, the Company issued 4,452,441 Series C-3 convertible redeemable preferred shares ("Series C-3 Preferred Shares") to a certain investor at US$11.23 per share for a total consideration of US$50,000,000.

Series C-1 Preferred Shares, Series C-2 Preferred Shares and Series C-3 Preferred Shares are collectively referred to as the Series C Preferred Shares.

Upon completion of the IPO on February 11, 2021, each of the then outstanding Series A Preferred Shares, Series B Preferred Shares, and Series C Preferred Shares (collectively the "Preferred Shares") was automatically converted into one ordinary share. As of December 31, 2021 and 2022, there were no preferred shares issued or outstanding.

Accounting for Preferred Shares

The Preferred Shares were classified as mezzanine equity in the consolidated balance sheets because they were contingently redeemable upon the occurrence of an event outside of the Company's control (e.g. the Company not achieving a Qualified Public Offering or a deemed liquidation event before March 31, 2025 ("Target QIPO Date")). The Preferred Shares were determined to be mezzanine equity with no embedded feature to be bifurcated and no beneficial conversion features to be recognized. The Preferred Shares were initially recorded at their respective issuance date fair value, net of issuance cost and fair value allocated to the detachable warrants. The Company did not incur material issuance cost for any Preferred Shares issued.

Prior to the IPO, the Company concluded that the Preferred Shares were not redeemable, but were probable to become redeemable. The Company accreted changes in the redemption value over the period from the date of issuance to the earliest redemption date for the year ended December 31, 2020, and to the IPO date for the year ended December 31, 2021, using the interest method. No accretion charge was recorded as the redemption value was fixed to original issue price for the periods presented, except for Series C-1 Preferred Shares issued with detachable warrants.

Modification of Preferred Shares

The Company made several amendments to the Preferred Shares, mainly including: 1) added redemption rights for Series A Preferred Shares upon the issuance of the Series B Preferred Shares; and 2) extended the Target QIPO Date upon the issuance of the Series C-1 Preferred Shares and the Series C-3 Preferred Shares. These amendments were accounted for as modifications rather than extinguishments as the fair values of these Preferred Shares immediately after the amendments were not significantly different from their respective fair values immediately before the amendment. When Preferred Shares are modified and such modification results in value transfer between preferred shareholders and ordinary shareholders, the value transferred is treated as a deemed dividend to or deemed contribution from the preferred shareholders.

The Company's Preferred Shares activities for the periods presented were summarized below:

Mezzanine equity	Series A-1	Series A-2	Series B	Series C-1	Series C-2	Series C-3	Total
	US$	US$	US$	US$	US$	US$	US$
Balance as of December 31, 2019	5,473,957	3,000,000	27,999,995	48,727,343	18,999,999	50,000,000	154,201,294
Accretion of Series C-1 Preferred Shares to redemption value	—	—	—	248,113	—	—	248,113
Balance as of December 31, 2020	5,473,957	3,000,000	27,999,995	48,975,456	18,999,999	50,000,000	154,449,407
Accretion of Series C-1 Preferred Shares to redemption value				28,553			28,553
Conversion of Preferred Shares to Ordinary Shares	(5,473,957)	(3,000,000)	(27,999,995)	(49,004,009)	(18,999,999)	(50,000,000)	(154,477,960)
Balance as of December 31, 2021	—	—	—	—	—	—	—

9. SHARE-BASED COMPENSATION

On November 7, 2015, the Company adopted a share incentive plan (the "2015 Plan"). Under the 2015 Plan, the Company's Board of Directors has approved that a maximum aggregate number of shares that may be issued pursuant to all awards granted shall be 4,336,126. In September 2017, the Company replaced the 2015 Plan with the amended and restated share incentive plan (the "2017 Plan") and increased the maximum number of shares issuable to 6,336,126. In December 2019, the Company replaced the 2017 Plan with the second amended and restated share incentive plan (the "2019 Plan") and further increased the maximum number of shares issuable to 11,391,131. The terms of the 2015 Plan, 2017 Plan and 2019 Plan are substantially the same other than the maximum aggregate number of shares the Company may issue under the respective plan.

Share options containing only service conditions granted to each grantee under the share incentive plan will generally be exercisable upon the grantee renders service to the Company in accordance with a stipulated vesting schedule. Grantees are generally subject to a vesting schedule of no longer than five years, under which the grantee earns an entitlement to vest a certain percentage of his option grants at the end of each month or year of completed service. The share option awards shall expire no more than 10 years from their grant dates.

Share options containing both service conditions and performance conditions granted to each grantee under the share incentive plan shall become eligible for vesting upon the occurrence of their applicable performance conditions (including but not limited to the occurrence of an IPO, the completion of business and operational goals, etc.).

On August 15, 2020, pursuant to a board resolution, 184,692 share options that granted to a senior management was modified and the vesting period of such share options was shortened from 5 years to 4 years. Since the fair value of the modified award was lower than the fair value of the original award immediately before the modification, no incremental compensation cost was recognized for the modification during the year ended December 31, 2021.

On November 9, 2020, the Company passed a board resolution to waive the vesting schedules and conditions of2,375,000 share options granted to certain management members. Pursuant to this board resolution, these management members exercised all related share options at the original exercise price per share ranging from US$1.83 to US$2.26. As a result, 2,375,000 ordinary shares were issued to these management members. These management members paid the exercise price by issuing recourse promissory notes in the total amount of US$5,197,650. The Company had the repurchase right to buy back such shares at the original exercise price if the grantees did not meet the original vesting conditions. The Company assessed and considered that in accordance with guidance set out in ASC 718-10-55-31, given such arrangement allows the shares received on exercise be returned to the Company if the original vesting conditions are not satisfied, there has been no substantial change to the vesting conditions and the Company shall continue to account for the share awards in accordance with their original terms. As of December 31, 2021, there were 1,585,000 shares unvested according to the original vesting conditions.

On January 16, 2021, the Company passed a board resolution whereby certain management members surrendered a total of 491,119 ordinary shares as repayment for their respective promissory notes issued in connection with the exercising of options granted to them. In the meantime, the Company further granted these management members the right to repurchase the surrendered shares by way of new option grants with an exercise price of US$13.85 per share. The fair values of these share options were US$7.85 per option, determined by using the binomial option valuation model. The share-based compensation expense related to these share options were recognized immediately upon grants.

Pursuant to the same board resolution, the 2021 Performance Incentive Plan (the "2021 Plan") was also adopted, under which an aggregate of2,994,000 ordinary shares shall be reserved for issuance, and the share limit will automatically increase on the first trading day in January of each year (commencing with 2022) by an amount equal to (1) 5% of the total number of the Company's outstanding ordinary shares on December 31 of the prior year, or (2) such lesser number as determined by the board of directors. From March 12, 2021 to December 22, 2021, pursuant to the 2021 Plan, a total of 1,303,000 share options were granted to certain employees by 15 batches, with exercise price ranging from US$5.92 to US$17.56, respectively. In addition, 23,734 ordinary shares were issued to certain management personnel on March 16, 2021 pursuant to the 2021 Plan.

On January 7, 2022, the Company passed a board resolution, pursuant to which the vesting schedules and conditions of2,060,308 share options granted to certain employees were modified. The share options vested (or to be vested) for each year (commencing from 2021) shall be equal to the lesser of (i) 25% of the total number of share options of each grantee ("Annual Cap") and (ii) the number of shares as determined by the Compensation Committee based on the extent to which any performance milestones were achieved during that year ("Credited Shares"), plus any Credited Share of earlier years that have not previously vested due to the Annual Cap. In addition, the performance milestones applicable to the share options that remain outstanding were also modified. As a result of the modification, the Company recognized an incremental fair value of US$2,337,697.

From February 7, 2022 to December 27, 2022, pursuant to the 2021 Plan, a total of2,640,598 share options were granted to certain employees, with exercise price ranging from US$0.80 to US$5.60, respectively. In addition, 99,999 ordinary shares were issued to certain management personnel on March 8, 2022 pursuant to the 2021 Plan.

As of December 31, 2021 and 2022, among all the share options granted to date, 2,483,808 and 4,776,906 share options contained both service conditions and performance conditions, respectively. All other share options granted contain only service conditions.

	Number of Options	Weighted-Average Exercise Price	Weighted-Average Grant Date Fair Value	Weighted Average Remaining Contractual Term	Aggregate Intrinsic Value
		US$ per option	US$ per option	Years	US$
Outstanding at December 31, 2019	866,028	0.65	3.67	7.27	6,328,171
Granted	6,313,373	2.00	7.01	—	—
Exercised	(3,694,934)	1.93	6.55	—	—
Forfeited	(190,000)	1.70	6.91	—	—
Outstanding at December 31, 2020	3,294,467	1.75	6.65	8.78	33,410,968
Granted	1,894,119	12.31	8.39	—	—
Exercised	(233,958)	0.99	5.13	—	—
Forfeited	(145,550)	3.02	7.71	—	—
Outstanding at December 31, 2021	4,809,078	5.91	7.38	8.68	2,619,574
Granted	2,640,598	3.28	2.13	—	—
Exercised	(197,975)	2.08	6.95	—	—
Forfeited	(964,789)	6.75	7.57	—	—
Outstanding at December 31, 2022	6,286,912	4.80	5.16	8.44	94,990
Vested and expected to vest at December 31, 2022	6,286,912	4.80	5.16	8.44	94,990
Exercisable at December 31, 2021	1,486,318	5.87	7.05	8.20	874,180
Exercisable at December 31, 2022	2,070,533	6.35	6.87	7.62	55,880

The aggregate intrinsic value in the table above represents the difference between the exercise price of the awards and the fair value of the underlying ordinary shares at each reporting date, for those awards that had exercise price below the estimated fair value of the relevant ordinary shares.

The aggregate fair value of the equity awards vested during the years ended December 31, 2020, 2021, and 2022 was US$8,430,085, US$13,833,856 and US$11,929,903, respectively. As of December 31, 2022, the total unrecognized employee share-based compensation expense was US$23,635,444, all of which may be adjusted for actual forfeitures occurring in the future. Total unrecognized compensation cost will be recognized over a weighted-average period of 2.20 years as of December 31, 2022.

Fair value of share options

The fair value of share options was determined using the binomial option valuation model, with the assistance from an independent third-party appraiser. The binomial model requires the input of highly subjective assumptions, including the expected volatility, the exercise multiple, the risk-free rate and the dividend yield. For expected volatility, the Group has made reference to historical volatility of several comparable companies in the same industry. The exercise multiple was estimated as the average ratio of the stock price to the exercise price of when employees would decide to voluntarily exercise their vested share options. The risk-free rate for periods within the contractual life of the share options is based on the market yield of U.S. Treasury Bonds in effect at the time of grant. The dividend yield is based on the expected dividend policy over the contractual life of the share options.

The assumptions used to estimate the fair value of the share options granted were as follows:

	For the years ended December 31,		
	2020	**2021**	**2022**
Risk-free interest rate	0.68% - 0.83%	1.11% - 1.67%	1.92% - 4.25%
Dividend yield	0%	0%	0%
Expected volatility range	72.3% - 73.4%	73.1% - 75.5%	74.2% - 74.9%
Exercise multiple	2.2 - 2.8	2.2 - 2.8	2.2 - 2.8
Contractual life	10 years	10 years	10 years

Total share-based compensation expenses recognized for the years ended December 31, 2020, 2021 and 2022 were as follows:

	For the years ended December 31,		
	2020	**2021**	**2022**
	US$	**US$**	**US$**
Research and development expenses	6,472,083	13,582,746	7,227,298
Administrative expenses	3,657,458	5,096,912	3,292,984
Total share-based compensation expenses	10,129,541	18,679,658	10,520,282

10. COLLABORATION ARRANGEMENTS

Guilin Sanjin Pharmaceutical Co., Ltd. License Agreement

In December 2018, the Group entered into (i) a collaboration agreement (the "Sanjin Greater China Agreement") that covers Greater China with Guilin Sanjin Pharmaceutical Co., Ltd. ("Sanjin") and certain of its subsidiaries (collectively, "Sanjin Parties") and (ii) a collaboration agreement (the "Sanjin ROW Agreement," together with the Sanjin Greater China Agreement, the "2018 Sanjin Agreements") that covers the regions other than Greater China with Sanjin. Pursuant to the Sanjin Greater China Agreement, the Group licensed the Chinese intellectual property directly related to a monospecific antibody molecule that binds to the PD-L1 target (the "PD-L1 Project"), including patent rights, patent application rights and technologies based on the core sequence of the molecule, to Sanjin Parties. Sanjin Parties will own all the Chinese intellectual property developed in the exercise of Sanjin Parties' rights under the agreement, including but not limited to improvements (including combination products), clinical trials, regulatory filings, and commercialization rights relating thereto. The Group also granted Sanjin Parties a royalty-free license to use our other existing intellectual property and improvements thereto which are related to the PD-L1 Project for the purposes of exploiting its rights and performing its obligations under the agreement. Sanjin Parties will enjoy all the economic benefits deriving from the PD-L1 Project in Greater China, including but not limited to patent transfer fee, licensing fee, sales revenue and sales commission, etc. Sanjin Parties will pay the Group (i) single-digit percentage of net sales of the products that use the licensed antibody after such products enter the market and (ii) a low to mid-low double-digit percentage of the profits resulting from any transfer of the license to any third parties depending on the timing of the transfer relative to the development stage of the product. The Group also received RMB10,000,000 (equivalent to approximately US$1,511,168) upfront fee upon the effectiveness of the agreement from Sanjin Parties, which was recognized as revenue in 2018. No revenue related to this agreement has been recognized in any of the years presented in the accompanying financial statements

Pursuant to the Sanjin ROW Agreement, the Group granted Sanjin a royalty-free license to use all intellectual property relating to (i) the collaboration under the agreement that the Group controlled before the Group entered into the agreement or acquired independently of the agreement and (ii) improvements thereto for the purposes of exploiting its rights and performing its obligations under the agreement. Any intellectual property generated independently by a party under the agreement will be solely owned by that party who generated such intellectual property, and any intellectual property generated from cooperation between the Group and Sanjin's affiliates in connection with the collaboration will be jointly owned. The Group retain the ownership of patent rights of key intellectual property pertaining to PD-L1 outside of the Greater China. In addition, all the results obtained by Sanjin relating to the research and development of any new antibody developed under the agreement will be owned by Sanjin. The Group retain a majority of the economic benefits derived from the Sanjin ROW Agreement, including but not limited to any patent transfer fee, licensing fee and gains realized under such transfer. In case the Group intend to transfer to a third party our share of economic interests in any country outside of Greater China, the Group must notify Sanjin and Sanjin will receive a right of first refusal if it pays the Group a deposit equal to a low double-digit percentage of the consideration that the Group expect to receive from such third party. If Sanjin waives the right of first refusal, the Group can proceed with the transfer, provided that the final transaction price with the third party is not lower than the amount of the offering price that was included in the Group's notice to Sanjin.

The Group agreed not to (i) independently develop any monospecific antibodies that bind to the PD-L1 target or (ii) grant any rights associated with such antibodies to any third parties during the three-year period from the effective date of the agreement. The exclusivity obligation does not prevent the Group from (i) developing or granting any licenses to third parties for intellectual property that covers bispecific antibodies, ADCs, diagnostic antibodies, nano-particles and masked antibody against PD-L1 target and (ii) continuing to provide antibody screening service that were commenced before the execution of the Sanjin Greater China Agreement and either party has the independent right to conduct combination therapy studies outside of the Greater China. Either non-breaching party may terminate the 2018 Sanjin Agreements if the other party's ability to comply with its respective obligations under the agreements is negatively affected by contingencies such as failure to maintain operation or changes in core project management and the other party fails to take effective remedial measures. Each agreement automatically terminates upon the termination of the other agreement. Upon the rescission or termination, Sanjin Parties will return to the Group all the intellectual property, documents and data provided by the Group under the 2018 Sanjin Agreements.

In the event that the failure of the development of the product candidate solely arises from the Group's research and development basis specified under this agreement, Sanjin has the right to claim back all the payment made to the Group. The Group considers the possibility of occurrence of such event is remote.

Dragon Boat Biopharmaceutical (Shanghai) Limited License Agreement

In May 2019, the Group entered into (i) a collaboration agreement that covers Greater China (the "Dragon Boat Greater China Agreement") and (ii) a collaboration agreement that covers the regions other than Greater China (the "Dragon Boat ROW Agreement," together with the Dragon Boat Greater China Agreement, the "2019 Dragon Boat Agreements"), with Dragon Boat Biopharmaceutical (Shanghai) Limited ("Dragon Boat"), a subsidiary of Sanjin. Pursuant to the Dragon Boat Greater China Agreement, the Group will license the Chinese intellectual property directly related to a certain monospecific antibody molecule that binds to a specified target (the "Specified Project"), including the patent rights, patent application rights and technologies based on the core sequence of the molecule, to Dragon Boat. Dragon Boat will own all the Chinese intellectual property developed in the exercise of Dragon Boat's rights under the agreement, including but not limited to improvements (including combination products), clinical trials, regulatory filings, and commercialization rights relating thereto. The Group also granted Dragon Boat a royalty-free license to use our other existing intellectual property and improvements thereto which are related to the Specified Project for the purposes of exploiting its rights and performing its obligations under the agreement. Dragon Boat will enjoy all the economic benefits deriving from the Specified Project in Greater China, including but not limited to patent transfer fee, licensing fee, sales revenue and sales commission, etc. and will pay the Group (i) certain high-six figure dollar milestone payments upon the achievement of certain milestones (including milestones of launch of pre-clinical safety evaluation animal test, obtaining Investigational New Drug ("IND") approval in PRC and completion of clinical phase I test in PRC) and (ii) a single-digit percentage of net sales of the products that use the licensed antibody after such products enter the market.

Pursuant to the Dragon Boat ROW Agreement, the Group granted Dragon Boat a royalty-free license to use all intellectual property relating to (i) the collaboration under the agreement that the Group controlled before the Group entered into the agreement or acquired independently of the agreement and (ii) improvements thereto for the purposes of exploiting its rights and performing its obligations under the agreement. Any intellectual property generated independently by a party under the agreement will be solely owned by that party who generated such intellectual property, and any intellectual property generated from cooperation between the Group and Dragon Boat in connection with the collaboration will be jointly owned. The Group retain the ownership of patent rights of key intellectual property pertaining to the specified target outside of the Greater China. In addition, all the results obtained by Dragon Boat relating to the research and development of any new antibody developed under the agreement will be owned by Dragon Boat. The Group retains a majority of the economic benefits derived from the Dragon Boat ROW Agreement, including but not limited to any patent transfer fee, licensing fee and gains realized under such transfer. In case the Group intend to transfer to a third party our share of economic interests in any country outside of Greater China, the Group must notify Dragon Boat and Dragon Boat will receive a right of first refusal if it pays the Group a deposit equal to a low double-digit percentage of the consideration that the Group expects to receive from such third party. If Dragon Boat waives the right of first refusal, the Group can proceed with the transfer, provided that the final transaction price with the third party is not lower than the amount of the offering price that was included in our notice to Dragon Boat.

Under the 2019 Dragon Boat Agreements, the Group agreed not to (i) independently develop any monospecific antibodies that bind to the specified target or (ii) grant any rights associated with such antibodies to any third parties during the three-year period from the effective date of the agreements. The exclusivity obligation does not prevent the Group from (i) developing or granting any licenses to third parties for intellectual property that covers bispecific antibodies, ADCs, diagnostic antibodies, nano-particles and masked antibody against the specific target and (ii) continuing to provide antibody screening service that were commenced before the execution of the Dragon Boat Greater China Agreement and either party has the independent right to conduct combination therapy studies outside of the Greater China. Either nonbreaching party may terminate the 2019 Dragon Boat Agreements if the other party's ability to comply with its obligations under the agreements is negatively affected by contingencies such as failure to maintain operation or changes in core project management and the other party fails to take effective remedial measures. Each agreement automatically terminates upon the termination of the other agreement. Upon the rescission or termination, Dragon Boat will return to the Group all the intellectual property, documents and data provided by the Group under the 2019 Dragon Boat Agreements.

In the event that the failure of the development of the product candidate solely arises from the Group's research and development basis specified under this agreement, Dragon Boat has the right to claim back all the payment made to the Group. The risk of failure is considered remote upon recognition of revenue.

For the year ended December 31, 2019, no revenue was recognized for this agreement since the licensed product has not been transferred to Dragon Boat.

As of December 31, 2020, upfront fee of RMB4,000,000 (equivalent to approximately US$573,378) that was received by the Group was recorded as contract liabilities in the consolidated balance sheets, as the performance obligation had not been satisfied by the Group and no revenue was recognized.

During the year ended December 31, 2021, milestone fee of RMB4,000,000 (equivalent to approximately US$620,011) was received related to the launch of pre-clinical safety evaluation animal test and the receipt of IND approval in PRC. For the year ended December 31, 2021, a total of RMB8,000,000 (equivalent to approximately US$1,240,022), including the aforementioned upfront fee and milestone fee were recognized as licensing revenue in the consolidated statement of comprehensive loss as the performance obligation was satisfied by the Group and certain milestone events were achieved.

No additional revenue was recognized for the year ended December 31, 2022.

ADC Therapeutics SA License and Collaboration Agreements

In April 2019, the Group entered into a material transfer and collaboration agreement (the "ADCT Collaboration Agreement") and a license agreement (the "ADCT License Agreement") with ADC Therapeutics SA ("ADC Therapeutics"). These two agreements are combined as a single contract as the agreements were negotiated as a package with a single commercial objective.

ADCT Collaboration Agreement

Pursuant to the ADCT Collaboration Agreement, the Group agreed to generate masked antibodies with respect to up to two exclusive targets selected by ADC Therapeutics. Upon our delivery of certain initial results, ADC Therapeutics has the option to license the Group's technology with respect to one or both targets as further detailed below. ADC Therapeutics has not yet exercised such options as of December 31, 2022.

Under the ADCT Collaboration Agreement, the Group is eligible to receive up to a low-seven-figure dollar amount in consideration for the Group's exclusivity obligations, upon achievement of certain development milestones (including milestones of delivery of certain amino acid sequences and successful outcome of the first in-vivo study) and upon ADC Therapeutics' election to proceed with development for the two elected targets. Apart from performance obligation to deliver the amino acid sequences of the corresponding masking peptides, the Group is not required to perform any additional research and development services. ADC Therapeutics has the right to terminate the ADCT Collaboration Agreement at any time and for any reason in its entirety or on a target-by-target basis upon thirty days' prior written notice to the Group. Either party may terminate the ADCT Collaboration Agreement, in its entirety or on a target-by-target basis, upon the other party's uncured material breach of the agreement or the other party's insolvency-related events.

The Group also granted ADC Therapeutics an exclusive target reservation right for one year from the commencement of the agreement and an option to renewal for another year with a consideration of low-six-figure dollar amount.

ADCT License Agreement

Subject to the exercise of the options contained in the ADCT Collaboration Agreement, the Group has granted ADC Therapeutics, with respect to each elected target, an exclusive, worldwide, perpetual and irrevocable (subject only to the termination provisions) license (with the right to grant sublicenses) to develop, make, use, commercialize and import the antibody drug conjugates that comprise masked antibodies generated by the Group under these programs.

Under the ADCT License Agreement, if ADC Therapeutics exercises both of its options granted thereunder, the Group could be eligible to receive up to a low-nine-figure dollar amount in development and regulatory milestone payments upon the achievement of certain milestones (including milestones of successful completion of Good Laboratory Practice Toxicology studies, launch of clinical trials and start of commercial sales in difference countries and etc.) and up to a mid-eight-figure dollar amount in sales milestone payments, in addition to mid-single-digit percentage net sales-based tiered royalties on products licensed under the ADCT License Agreement, subject to certain reductions. Royalties, if any, will be payable on a country-by-country and product-by-product basis, until the earlier of (i) the tenth anniversary of the first commercial sale of such product or (ii) the expiration of the last-to-expire patent licensed under the agreement in such country, unless earlier terminated by the parties, following which any licenses granted to ADC Therapeutics under the ADCT License Agreement shall become fully paid up, perpetual and irrevocable.

ADC Therapeutics has the right to terminate the ADCT License Agreement before the expiration of the royalty term on a product-by-product basis or in its entirety (i) for any reason or no reason upon thirty days' written notice to the Group, or (ii) if ADC Therapeutics chooses to discontinue the development or sale of the applicable licensed product worldwide. Each party has certain rights to terminate the ADCT License Agreement with prior written notice upon the other party's uncured material breach or insolvency.

For the year ended December 31, 2020, the Group recognized US$225,000 of licensing revenue upon delivery of such results. For the year ended December 31, 2020, the Group recognized US$100,000 as other income due to the expiration of exclusive target reservation right, which is not related to the Group's major operation activity.

For the year ended December 31, 2021, the Group recognized US$225,000 of licensing revenue upon delivery of additional research results.

For the year ended December 31, 2022, the Group did not recognize additional revenue associated with the agreements.

ADCT Material Transfer and Option Agreement

In August 2022, the Group entered into a material transfer and option agreement (the "ADCT Material Transfer and Option Agreement") with ADCT. Under the agreement, Adagene agreed to provide antibodies or antibody sequences to ADCT to conduct further development for a non-refundable fee of US$300,000. ADCT has an exclusive option to negotiate a separate license agreement with the Group, however, there is no requirement for either party to enter into such a license agreement.

For the year ended December 31, 2022, the Group recognized revenue of US$300,000, which was received in October 2022, upon delivery of the sequences.

Exelixis, Inc. Agreements

In February 2021, the Group entered into a collaboration and license agreement (the "Exelixis Agreement") with Exelixis, Inc. ("Exelixis"), pursuant to which the Group agreed to generate masked antibodies with its SAFEbody technology against an initial target selected and a second target to be selected by Exelixis. The Group will generate masked antibodies in the form of alternative compounds in accordance with the program plan for each target at its own cost and deliver the related data packages to Exelixis. Exelixis will select lead compounds (the "Lead Compounds") to further develop, obtain regulatory approval and commercialize product(s) for each target (the "Products under the Exelixis Agreement"). Under the Exelixis Agreement, the Group will also grant Exelixis an exclusive, worldwide, sublicensable license (the "Adagene License") upon delivery of the data package to research, develop, make, have made, sell, offer for sale, import and commercialize products containing the masked antibodies to be generated by the Group with respect to both targets. Exelixis will own the inventions relating to the Lead Compounds arising in connection with the Exelixis Agreement.

The Exelixis Agreement will remain effective until the expiration of the defined royalty terms of the Products under the Exelixis Agreement, unless terminated by either party. Exelixis may terminate the Exelixis Agreement for any or no reason, in its entirety or on a target-by-target basis. Any payment received by the Group before the termination shall be non-refundable.

Under the Exelixis Agreement, Exelixis agreed to pay the Group an upfront non-refundable fee of US$11,000,000. For each target, the Group will be eligible to receive up to US$127,500,000 of milestone payments conditioned upon achieving certain development and regulatory approval milestones, and up to $262,500,000 of sales-based milestone payments. In addition, the Group is also entitled to royalties of mid-single-digit percentage in respect of the aggregate annual net sales of the products developed under the Exelixis Agreement worldwide, subject to certain reductions.

In April 2022, the Group entered in a letter agreement (the "Exelixis Letter Agreement") in reference to the Exelixis Agreement with Exelixis for expanded collaboration in SAFEbody discovery. Under the Exelixis Letter Agreement, the Group will generate additional masked antibodies against the target selected by Exelixis per the Exelixis Agreement. Exelixis agreed to pay the Group an additional upfront non-refundable fee of US$1,100,000.

The Group determined that generating masked antibodies with its SAFEbody technology is reflective of a vendor-customer relationship and therefore within the scope of ASC 606. Under the Exelixis Agreement, the delivery of data packages for each target, along with the Adagene License used to develop the related compounds, represents one performance obligation, as they are not distinct from each other. Transaction price is allocated to each one of the two performance obligations using the relative standalone selling price method. The Group records revenue at a point in time, when the data packages for each target were delivered to Exelixis. Considering that the development, regulatory and sales-based milestone payments and the royalties are constrained, the transaction price shall initially only include upfront payment and the milestone payments that are considered probable. Subsequently, once the uncertainty associated with the milestone payments is resolved, the milestone payments shall be included in the total transaction price when it is no longer probable that a significant reversal of cumulative revenue would occur in future periods. The sales-based royalty and sales-based milestones promised in exchange for the Adagene License granted are recognized when (or as) the later of (1) the subsequent sale or usage occurs, or (2) the performance obligation to which some or all of the sales-based royalty or sales-based milestones being allocated has been satisfied (or partially satisfied).

For the year ended December 31, 2021, the Group received US$11,000,000 upfront payment and recorded accounts receivable of US$3,000,000 milestone payment, which corresponds to the successful nomination of lead SAFEbody candidates for the initial target under the Exelixis Agreement. The milestone payment was subsequently received in January 2022. For the year ended December 31, 2021, US$8,500,000 was recognized as revenue upon delivery of data packages for the initial target and achievement of the milestone event.

For the year ended December 31, 2022, the Group received US$1,100,000 upfront payment under the Exelixis Letter Agreement. No additional revenue was recognized as relevant performance obligation has yet to be fully satisfied under either the Exelixis Agreement or the Exelixis Letter Agreement.

Sanofi Agreement

In March 2022, the Group entered into a collaboration and license agreement (the “Sanofi Agreement”) with Genzyme Corporation, a wholly-owned subsidiary of Sanofi (“Sanofi”), pursuant to which the Group agreed to perform early-stage research activities to develop masked versions of Sanofi candidate antibodies (each a “Target”, and together, “Targets”), using Adagene’s SAFEbody technology for development and commercialization by Sanofi. Sanofi has the ability to advance two initial Targets in the collaboration, followed by an option for two additional Targets. The Group will generate masked antibodies in the form of customized compounds and complete the compound research activities in accordance with the program plan for each Target at its own cost and deliver the compounds and related data packages to Sanofi. Sanofi is solely responsible for later stage research and all clinical, product development and commercialization activities. Under the Sanofi Agreement, the Group granted Sanofi an exclusive, worldwide, sublicensable license to research, develop, use, make, have made, sell, offer for sale, import and commercialize products containing the masked antibodies to be generated by the Group.

The Sanofi Agreement will remain effective until the expiration of the defined royalty on a product-by-product and country-by-country basis, unless terminated earlier with cause or by mutual agreements of both parties. Sanofi may terminate the Sanofi Agreement without cause, in its entirety, or on a Target-by-Target or country-by-country basis.

Under the Sanofi Agreement, Sanofi agreed to pay the Group an upfront non-refundable fee of US$17,500,000 in consideration of the license granted and the early-stage research activities to generate the compounds. Sanofi is obligated to pay an additional fee if Sanofi exercises the option for additional Targets. For each Target, the Group will be eligible to receive up to US$173,500,000 of milestone payments conditioned upon achieving certain development and regulatory approval milestones, and up to $450,000,000 of sales-based milestone payments. In addition, the Group is also entitled to royalties of mid-single-digit percentage in respect of the aggregate annual net sales of the products developed under the Sanofi Agreement worldwide, subject to certain reductions.

The Group then determined that this collaboration is more reflective of a vendor-customer relationship and therefore within the scope of ASC 606. Under the Sanofi Agreement, the performance of early-stage research activities to develop compounds for each Target, along with the grant of the license, represents one performance obligation, as they are not distinct from each other. Transaction price is allocated to each one of the two performance obligations based on the relative standalone selling price. Since the early-stage research activities does not generate an asset for alternative use and the Group has an enforceable right to the upfront payment, the Group records revenue over time using labor hour as the input to assess the satisfaction of the performance obligations. Considering that the development, regulatory and sales-based milestone payments and the royalties are constrained, the transaction price shall initially only include upfront payment and the milestone payments that are considered probable. Subsequently, once the uncertainty associated with the milestone payments is resolved, the milestone payments shall be included in the total transaction price when it is no longer probable that a significant reversal of cumulative revenue would occur in future periods. The sales-based royalty and sales-based milestones promised in exchange for the license granted are recognized when (or as) the later of (1) the subsequent sale or usage occurs, or (2) the performance obligation to which some or all of the sales-based royalty or sales-based milestones being allocated has been satisfied (or partially satisfied).

For the year ended December 31, 2022, the Group received US$17,500,000 upfront payment under the Sanofi Agreement. For the year ended December 31, 2022, US$8,992,724 was recognized as revenue over time using the input method.

11. INCOME TAX EXPENSE

PRC

Effective from January 1, 2008, the PRC's statutory, Enterprise Income Tax ("EIT") rate is 25%. In accordance with the implementation rules of EIT Law, a qualified "Technology Advanced Service Enterprises" ("TASE") is eligible for a preferential tax rate of 15%. The TASE certificate is effective for three years. An entity must file required supporting documents with the tax authority and ensure fulfillment of the relevant TASE criteria before using the preferential rate. An entity could apply for the TASE certificate every year. Dividends by PRC entities, to non-PRC resident enterprises shall be subject to 10% EIT, namely withholding tax, unless the respective non-PRC resident enterprise's jurisdiction of incorporation has a tax treaty or arrangements with China that provides for a reduced withholding tax rate or an exemption from withholding tax.

Adagene (Suzhou) Limited was first recognized as a qualified TASE in March 2015 and renewed in December 2018 and November 2021. Adagene (Suzhou) Limited was authorized to enjoy the preferential tax rate of 15% from 2015 to at least 2023.

Cayman Islands

Adagene Inc. is incorporated in the Cayman Islands. Under the current laws of the Cayman Islands Adagene Inc. is not subject to tax on income or capital gain. Additionally, the Cayman Islands does not impose a withholding tax on payments of dividends to shareholders.

Hong Kong

Adagene (Hong Kong) Limited is incorporated in Hong Kong. Companies registered in Hong Kong are subject to Hong Kong profits tax on the taxable income as reported in their respective statutory financial statements adjusted in accordance with the relevant Hong Kong tax laws. The applicable tax rate in Hong Kong is 16.5%. For the years ended December 31, 2020, 2021 and 2022, Adagene (Hong Kong) Limited did not make any provisions for Hong Kong profit tax as there were no assessable profits derived from or earnings in Hong Kong for any of the periods presented. Under the Hong Kong tax law, Adagene (Hong Kong) Limited is exempted from income tax on its foreign-derived income and there are no withholding taxes in Hong Kong on remittance of dividends.

Australia

Adagene Australia Pty Ltd. is incorporated in Australia. Companies registered in Australia are subject to Australia profits tax on the taxable income as reported in their respective statutory financial statements adjusted in accordance with the relevant Australia tax laws. The applicable tax rate in Australia is 30%. Adagene Australia Pty Ltd. has no taxable income for all periods presented, therefore, no provision for income taxes is required. Dividends payable by an Australian entity, to non-Australian resident enterprises shall be subject to 30% withholding tax, unless the respective non-Australian resident enterprise's jurisdiction of incorporation has a tax treaty or arrangements with Australia that provides for a reduced withholding tax rate or an exemption from withholding tax.

United States

Adagene Incorporated is incorporated in U.S. and is subject to U.S. federal corporate income tax at a rate of 21%. Adagene Incorporated is also subject to state income tax in California of 8.84%. Dividends payable by an U.S. entity, to non-U.S. resident enterprises shall be subject to 30% withholding tax, unless the respective non-U.S. resident enterprise's jurisdiction of incorporation has a tax treaty or arrangements with U.S. that provides for a reduced withholding tax rate or an exemption from withholding tax.

Switzerland

Adagene AG is incorporated in Switzerland and is subject to federal corporate income tax at a rate of 8.5%. Adagene AG is also subject to cantonal income tax of 6.5% as well as capital tax of 0.1% in the Canton of Basel subject to certain tax benefits and relief. Dividends payable by a Swiss entity, to non-Swiss resident enterprises shall be subject to 35% withholding tax, unless the respective non-Swiss resident enterprise's jurisdiction of incorporation has a tax treaty or arrangements with Switzerland that provides for a reduced withholding tax rate or an exemption from withholding tax.

Income tax expense (benefit) of the Group for the years ended December 31, 2020, 2021 and 2022 were composed of the following current and deferred amounts:

	For the years ended December 31,		
	2020	2021	2022
	US$	US$	US$
Current:			
U.S.			
Federal	—	1,290,009	672,064
State and local	—	367,441	(168,846)
Total current	—	1,657,450	503,218
Deferred:			
U.S.			
Federal	—	96,804	(96,804)
State and local	—	(52,641)	52,641
Total deferred	—	44,163	(44,163)
Income tax expense	—	1,701,613	459,055

Reconciliation between the income tax expense computed by applying the statutory tax rate to loss before income tax and the actual provision for income tax was as follows:

	For the years ended December 31,		
	2020	2021	2022
	US$	US$	US$
Loss before income tax	(42,397,279)	(71,476,322)	(79,512,792)
PRC statutory income tax rate	25 %	25 %	25 %
Income tax credit computed at PRC statutory income tax rate	(10,599,320)	(17,869,081)	(19,878,198)
Impact of PRC preferential income tax rate as qualified TASE	4,239,728	7,147,633	7,951,279
Difference in income tax rates of overseas entities	5,286,487	10,549,985	10,560,029
Research and development super-deduction[(a)]	(718,979)	(569,016)	(1,724,740)
Research and development tax credits	—	—	(569,575)
Non-deductible expenses	1,238	1,054	3,695
Foreign derived intangible income deduction	—	—	(487,183)
Changes in valuation allowance	1,790,846	2,277,418	4,517,358
State tax	—	291,500	76,127
Others	—	(127,880)	10,263
Income tax expense	—	1,701,613	459,055

Note (a): Due to the impacts of research and development super-deduction, the Group's subsidiary, Adagene (Suzhou) Limited, did not have any income taxes for the years ended December 31, 2020, 2021, and 2022.

Deferred tax assets and liabilities

Deferred taxes were measured using the enacted tax rates for the periods in which the temporary differences are expected to be reversed. The tax effects of temporary differences that give rise to the deferred tax balances as of December 31, 2021 and 2022 were as follows:

	As of December 31,	
	2021	2022
	US$	US$
Deferred tax assets:		
Net operating loss carry forward	4,949,000	8,217,976
Tax credit carry forward	—	391,843
Capitalized research and development expenses	—	756,197
Capitalized inventory	95,589	94,954
Unrealized foreign exchange gain/losses	39,166	116,238
Accrued expenses	—	29,702
Amortization of right-of-use assets and interest of lease liabilities	—	546
Depreciation and amortization of property, equipment and software	79	—
Gross deferred tax assets	5,083,834	9,607,456
Less: valuation allowance	(5,007,139)	(9,524,497)
Deferred tax assets	76,695	82,959
Deferred tax liabilities:		
Depreciation and amortization of property, equipment and software	(120,858)	(82,959)
Deferred tax liabilities	(120,858)	(82,959)
Total deferred tax liabilities, net	(44,163)	—

Movement of the valuation allowance was as follows:

	2021	2022
	US$	US$
Balance as of January 1	2,729,721	5,007,139
Addition	2,277,418	4,517,358
Balance as of December 31	5,007,139	9,524,497

A valuation allowance is provided to reduce the amount of deferred tax assets if it is considered more likely than not that some portion or all of the deferred tax assets will not be realized in the foreseeable future. In making such determination, the Group evaluates a variety of positive and negative factors including the Group's operating history, accumulated deficit, the existence of taxable temporary differences and reversal periods.

The Group has incurred net accumulated operating losses for income tax purposes since its inception. As of December 31, 2022, the Group had net operating losses for income tax purpose of approximately US$50,742,841. The net operating losses were primarily comprised of: US$17,886,069 from an entity in PRC which expires in years 2028 through 2032; US$8,272,007 derived from an entity Switzerland which expires in years 2027 through 2029; US$5,445,071 derived from an entity in Hong Kong that have an indefinite carryforward; US$7,511,343 derived from an entity in Australia that have an indefinite carryforward subject to meeting certain criteria; US$10,807,828 derived from an entity in the United States which expires beginning year 2038; and, US$820,523 derived from entities in Singapore. The Group believes that it is more likely than not that these net accumulated operating losses will not be utilized in the near future. Therefore, the Group has provided full valuation allowances for the deferred tax assets for all subsidiaries as of December 31, 2022.

The Group evaluates each uncertain tax position (including the potential application of interest and penalties) based on the technical merits, and measure the unrecognized benefits associated with the tax positions. As of December 31, 2021 and 2022, the Group did not have any significant unrecognized uncertain tax positions. The Group does not anticipate that the amount of unrecognized tax benefits will significantly change within the next 12 months.

The Group conducts business in a number of tax jurisdictions and, as such, is required to file income tax returns in multiple jurisdictions globally. As of December 31, 2022, PRC tax matters are open to examination for the years 2020 through 2022, U.S. federal and state tax matters are open to examination for the years 2019 through 2022, and Australia tax matters are open to examination for the years 2019 through 2022.

12. NET LOSS PER SHARE

Basic and diluted net loss per share for the years ended December 31, 2020, 2021 and 2022 were calculated as follows:

	For the Year Ended December 31,		
	2020	2021	2022
	US$	US$	US$
Numerator:			
Net loss attributable to Adagene Inc.'s shareholders	(42,397,279)	(73,177,935)	(79,971,847)
Accretion of convertible redeemable preferred shares to redemption value	(248,113)	(28,553)	—
Net loss attributable to ordinary shareholders	(42,645,392)	(73,206,488)	(79,971,847)
Denominator:			
Weighted-average number of ordinary shares outstanding—basic and diluted	15,950,698	50,032,009	54,135,084
Net Loss per share—basic and diluted	(2.67)	(1.46)	(1.48)

The effects of all outstanding convertible redeemable preferred shares and share options have been excluded from the computation of diluted loss per share for the years ended December 31, 2020, 2021 and 2022 as their effects would be anti-dilutive.

The potentially dilutive securities that have not been included in the calculation of diluted net loss per share as their inclusion would be anti-dilutive are as follows:

	For the Year Ended December 31,		
	2020	2021	2022
Convertible redeemable preferred shares	27,249,824	—	—
Share options and share grant	1,795,932	1,739,882	530,298

13. RELATED PARTY TRANSACTIONS

a) Related Parties

Name of related parties	Relationship
Peter Luo	Chairman, Chief Executive Officer and a principal shareholder of the Company
Four senior management personnel	Management and ordinary shareholders of the Company
WuXi AppTec Co., Ltd. (“WuXi AppTec Group”)	A principal shareholder of the Company
WuXi Biologics (Cayman) Inc.	Controlled by the ultimate controlling party of a principal shareholder of the Company

b) The Group had the following related party balances as of December 31, 2021 and 2022:

	As of December 31,	
	2021	2022
	US$	US$
WuXi AppTec Group	3,080,116	503,941
WuXi Biologics (Cayman) Inc.	1,426,554	115,491
Total amounts due from related parties	4,506,670	619,432

As of December 31, 2021 and 2022, the amounts due from related parties represented prepayments made for the CRO and CMO services.

	As of December 31,	
	2021	2022
	US$	US$
WuXi Biologics (Cayman) Inc.	10,292,268	17,840,876
WuXi AppTec Group	173,793	1,482,461
Total amounts due to related parties	10,466,061	19,323,337

As of December 31, 2021 and 2022, the amounts due to related parties represented payables for the CRO and CMO services.

c) The Group had the following related party transactions during the years ended December 31, 2020, 2021 and 2022:

	For the years ended December 31,		
	2020	2021	2022
	US$	US$	US$
Receipt of CRO and CMO services:			
WuXi Biologics (Cayman) Inc.	7,217,709	12,561,276	27,764,750
WuXi AppTec Group	2,674,586	517,742	7,362,713
	9,892,295	13,079,018	35,127,463

14. LEASES

As of December 31, 2022, the Group has operating leases recorded on its consolidated balance sheet for certain office spaces that expire on various dates through 2024. The Group does not plan to cancel the existing lease agreements for its existing office spaces prior to their respective expiration dates. The Group's lease arrangements have no renewal options, rent escalation clauses, restrictions or contingent rents and are all executed with third parties. All of the Group's leases qualify as operating leases.

Information related to operating leases as of December 31, 2022 is as follows:

	As of December 31, 2022 US$
Assets	
Operating lease right-of-use assets	191,877
Liabilities	
Current portion of operating lease liabilities	151,983
Operating lease liabilities	53,834
Weighted average remaining lease term (years)	1.3
Weighted average discount rate	4.6 %

Information related to operating lease activity during the year ended December 31, 2022 is as follows:

	For the Year Ended December 31, 2022 US$
Operating lease rental expense	
Amortization of right-of-use assets	283,276
Expense for short-term leases within 12 months	34,729
Interest of lease liabilities	20,259
	338,264

Future annual minimum lease under non-cancelable operating leases with initial terms in excess of one year as of December 31, 2021 under ASC 840, *Leases*, were as follows:

	As of December 31, 2021 US$
For the years ending:	
2022	412,754
2023	255,309
2024	70,367
Total	738,430

Maturities of lease liabilities were as follows:

	As of December 31, 2022 US$
2023	157,603
2024	54,823
Total undiscounted lease payments	212,426
Less: imputed interest	(6,609)
Total lease liabilities	205,817

15. COMMITMENTS AND CONTINGENCIES

Contingencies

The Group is currently not involved in any legal or administrative proceedings that may have a material adverse impact on the Group's business, financial position or results of operations.

16. RESTRICTED NET ASSETS

The Group's ability to pay dividends may depend on the Group receiving distributions of funds from its PRC subsidiary. Relevant PRC statutory laws and regulations permit payments of dividends by the Group's PRC subsidiary only out of its retained earnings, if any, as determined in accordance with PRC accounting standards and regulations. The results of operations reflected in the consolidated financial statements prepared in accordance with U.S. GAAP differ from those reflected in the statutory financial statements of the Group's PRC subsidiary.

In accordance with the company law of the PRC, a domestic enterprise is required to provide statutory reserves of at least 10% of its annual after-tax profit until such reserve has reached 50% of its respective registered capital based on the enterprise's PRC statutory accounts. A domestic enterprise is also required to provide discretionary surplus reserve, at the discretion of the Board of Directors, from the profits determined in accordance with the enterprise's PRC statutory accounts. The aforementioned reserves can only be used for specific purposes and are not distributable as cash dividends. The Group's PRC subsidiary was established as domestic invested enterprise and therefore is subject to the abovementioned restrictions on distributable profits.

As of December 31, 2021 and 2022, the total restricted net assets of the Company's subsidiary incorporated in PRC and subjected to restriction amounted to approximately US$1,860,667 for both years. Other subsidiaries are not subjected to such restriction.

As a result of these PRC laws and regulations subject to the limit discussed above that require annual appropriations of 10% of after-tax income to be set aside, prior to payment of dividends, as general reserve fund, the Group's PRC subsidiary is restricted in their ability to transfer a portion of their net assets to the Group.

Foreign exchange and other regulations in the PRC further restrict the Group's PRC subsidiaries from transferring funds to the Company in the form of dividends, loans and advances.

As of December 31, 2022, the net asset base for purposes of calculating the proportionate share of restricted net assets of consolidated subsidiaries was US$1,860,667 from the PRC subsidiary, and the Group had a consolidated shareholders' equity. As the restricted net assets of consolidated subsidiaries do not exceed 25% of consolidated net assets as of the most recent fiscal year end, the Group is not required to provide parent company financial information.

17. Treasury Shares

The Group accounts for treasury shares using the cost method. Under this method, the cost incurred to purchase the shares is recorded in the treasury shares account in the consolidated balance sheets. At retirement, the ordinary shares account is charged only for the aggregate par value of the shares. The excess of the acquisition cost of treasury shares over the aggregate par value is recorded entirely in additional paid-in capital (up to the amount credited to the additional paid-in capital upon original issuance of the shares). In the event that treasury share is reissued at an amount different from the cost the Group paid to repurchase the treasury share, the Group will recognize the difference in additional paid-in capital by using the specified identification method.

On July 7, 2021, the Board of Directors approved a share repurchase program to repurchase up to US$20 million of outstanding ADSs of the Company, from time to time over a 12-month period from the date on which a formal stock repurchase plan engagement agreement was signed with a qualified broker-dealer (the "2021 Share Repurchase Program"). The 2021 Share Repurchase Program commenced on July 20, 2021. During the year ended December 31, 2021 and 2022, 236,139 and 1,170,446 outstanding ADSs (295,174 and 1,463,057 ordinary shares) were repurchased with a total consideration of US$2,361,576 and US$3,904,399 respectively, under the 2021 Share Repurchase Program.

On June 29, 2022, the Board of Directors authorized a share repurchase program to repurchase up to US$10 million of outstanding ADSs of the Company during a period of up to 12 months commencing on July 20, 2022 (the “2022 Share Repurchase Program”). The 2022 Share Repurchase Program was subsequently terminated in July 2022. During the year ended December 31, 2022, 39,900 outstanding ADSs (49,875 ordinary shares) was repurchased with a total consideration of US$72,282 under the 2022 Share Repurchase Program.

During the year ended December 31, 2021 and 2022, 160,880 and 1,285,604 ADSs (201,100 and 1,607,005 ordinary shares) repurchased have been retired , respectively. As of December 31, 2021 and 2022, there were 75,259 and 1 ADSs (94,074 and 1 ordinary shares) held as treasury shares, respectively.

18. SUBSEQUENT EVENTS

From January to April, 2023, a total of 582,630 ordinary shares were issued to certain management personnel pursuant to the 2021 Plan.