

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

A. [Reserved.]

B. Capitalization and Indebtedness.

Not applicable.

C. Reasons for the Offer and Use of Proceeds.

Not applicable.

D. Risk Factors.

Investing in American Depositary Shares representing our ordinary shares, or ADSs, involves a high degree of risk. You should carefully consider the following risk factors and all other information contained in this Annual Report, including our consolidated financial statements and the related notes, before investing in the ADSs. The risks and uncertainties described below are those significant risk factors, currently known and specific to us, that we believe are relevant to an investment in the ADSs. If any of these risks materialize, our business, results of operations or financial condition could suffer, the price of the ADSs could decline and you could lose part or all of your investment. Additional risks and uncertainties not currently known to us or that we now deem immaterial may also harm us and adversely affect your investment in the ADSs.

Risks Associated with Our Business

Our business is subject to a number of risks of which you should be aware before making an investment decision. You should carefully consider all of the information set forth in this report and, in particular, should evaluate the specific factors set forth in the section titled "Risk Factors" before deciding whether to invest in our ADSs. Among these important risks are, but not limited to, the following:

- Our need for substantial additional financial resources to continue as a going concern, continue ongoing development of our product candidates and pursue our business objectives; if we are unable to obtain these additional resources when needed, we may be forced to delay or discontinue our planned operations, including clinical testing of our product candidates.
- The approach we are taking to discover and develop drugs is novel and we may not be successful in our efforts to identify or discover potential drug product candidates to bring into clinical trials.
- If clinical trials of our product candidates fail to commence or, once commenced, fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities, or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.
- We have a history of net losses and we anticipate that we will continue to incur significant losses for the foreseeable future.

- We will need additional capital, which may not be available on acceptable terms, or at all.
- We face competition from other companies that are working to develop novel drugs and technology platforms using technologies similar to ours. If these companies compete with us for limited manufacturing supplies, or for animals critical for preclinical testing, or otherwise develop drugs more rapidly than we do, or their technologies, including delivery technologies, are more effective, our ability to successfully commercialize drugs may be adversely affected.
- We rely on third parties to conduct some aspects of our manufacturing, research and development activities, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of manufacturing, research or clinical testing.
- If we are unable to obtain or protect intellectual property rights related to our current or future product candidates, we may not be able to compete effectively in any or all markets.
- An active trading market for our ADSs may not develop and you may not be able to resell your ADSs at or above the price you pay for them, if at all.
- We qualify as a foreign private issuer and, as a result, we will not be subject to U.S. proxy rules and will be subject to Exchange Act reporting obligations that, to some extent, are more lenient and less frequent than those of a U.S. domestic public company.
- If equity research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business or our market, the price and trading volume of our ADSs could decline.
- If we are a passive foreign investment company, there could be adverse U.S. federal income tax consequences to U.S. Holders.
- The withdrawal of the United Kingdom from the European Union, commonly referred to as “Brexit,” may adversely impact our ability to obtain regulatory approvals of our product candidates in the European Union, result in restrictions or imposition of taxes and duties for importing our product candidates into the European Union, may require additional licenses and procedural steps and may require us to incur additional expenses in order to develop, manufacture and commercialize our product candidates in the European Union.
- The Ukraine/Russia War could adversely affect our operations, including increases in the prices of the supplies used in our business, supply chain interruptions and increased cybersecurity risks.
- Inflation may adversely affect our operations, including increases in the prices of goods and services required for our operations.

Implications of Being an Emerging Growth Company and a Foreign Private Issuer

Emerging Growth Company

We are an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As such, we may take advantage of certain exemptions from various reporting requirements that are applicable to other publicly traded entities that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act of 2002;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board, or PCAOB, regarding mandatory audit firm rotation or a supplement to the auditor’s report

providing additional information about the audit and the financial statements (i.e., an auditor discussion and analysis);

- not being required to submit certain executive compensation matters to shareholder advisory votes, such as “say-on-pay,” “say-on-frequency,” and “say-on-golden parachutes”; and
- not being required to disclose certain executive compensation related items such as the correlation between executive compensation and performance and comparisons of the chief executive officer’s compensation to median employee compensation.

We will remain an emerging growth company until the earliest of: (1) the last day of the first fiscal year in which our annual gross revenues exceed \$1.235 billion; (2) the last day of 2025; (3) the date that we become a “large accelerated filer” as defined in Rule 12b-2 under the Exchange Act, which would occur on the last day of any fiscal year that the aggregate worldwide market value of our common equity held by non-affiliates exceeds \$700 million as of the last business day of our most recently completed second fiscal quarter; or (4) the date on which we have issued more than \$1.0 billion in non-convertible debt securities during any three-year period.

Foreign Private Issuer

We report under the Exchange Act as a non-U.S. company with foreign private issuer status. Even after we no longer qualify as an emerging growth company, as long as we qualify as a foreign private issuer under the Exchange Act, we will be exempt from certain provisions of the Exchange Act that are applicable to U.S. domestic public companies, including:

- 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 rules under the Exchange Act requiring the filing with the SEC of quarterly reports on Form 10-Q containing unaudited financial and other specific information, and current reports on Form 8-K upon the occurrence of specified significant events.

Foreign private issuers are also exempt from certain more stringent executive compensation disclosure rules. Thus, even if we no longer qualify as an emerging growth company, but remain a foreign private issuer, we will continue to be exempt from the more stringent compensation disclosures required of companies that are neither an emerging growth company nor a foreign private issuer.

Risks Related to Our Financial Condition and Need for Additional Capital

We have a history of net losses and we anticipate that we will continue to incur significant losses for the foreseeable future.

We are a clinical-stage biopharmaceutical company. As of the date hereof, our operations have been primarily limited to developing our siRNA product platform, undertaking basic research around siRNA targets, conducting preclinical and clinical studies and out-licensing some of our intellectual property rights. We have not yet obtained marketing approval for any product candidates and may not for the foreseeable future, if ever. Consequently, any predictions about our future success or viability, or any evaluation of our business and prospects, may not be accurate.

We have incurred net losses in each year since our inception. Our net losses were £40.5 million for the year ended December 31, 2022, £39.4 million for the year ended December 31, 2021, and £32.5 million for the year ended December 31, 2020. As of December 31, 2022, we had an accumulated loss of £263.3 million. Our losses have resulted from costs incurred to research and development, including our preclinical and clinical development activities.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future, although these losses may fluctuate significantly between periods. We anticipate that our expenses will increase substantially as we continue the research, preclinical and clinical development of our product candidates, both independently and under our collaboration agreements with third parties. We would also incur additional expenses in connection with seeking marketing approvals for any product candidates that successfully complete clinical trials, if any, and establishing a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval. We will also need to maintain, expand and protect our intellectual property portfolio, hire additional personnel, and create additional infrastructure to support our operations and our product development efforts. We expect that all of these additional expenses will cause our total expenses to substantially exceed our revenue over the near term, resulting in continuing operating losses and increasing accumulated deficits.

We have never generated any revenue from product sales and may never be profitable.

Our ability to generate revenue and achieve profitability depends on our ability, alone or with collaboration partners, to successfully complete the development of, obtain the necessary regulatory approvals for and commercialize our product candidates. We do not anticipate generating revenues from sales of products for the foreseeable future, if ever. Our ability to generate future revenues from product sales will depend heavily on our success in:

- identifying and validating therapeutic targets;
- completing our research and preclinical development of product candidates;
- initiating and completing clinical trials for product candidates;
- seeking, obtaining and maintaining marketing approvals for product candidates that successfully complete clinical trials;
- establishing and maintaining supply and manufacturing relationships with third parties, or establishing our own manufacturing capability;
- launching and commercializing product candidates for which we obtain marketing approval, either with a collaborator or, if launched independently, successfully establishing a sales force, marketing and distribution infrastructure;
- maintaining, expanding and protecting our intellectual property portfolio; and
- attracting, hiring and retaining qualified personnel.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to predict the timing or amount of increased expenses and when we will be able to achieve or maintain profitability, if ever. In addition, our expenses could increase if we were required by the U.S. Food and Drug Administration, or FDA, the European Medicines Agency, or EMA, the U.K. Medicines and Healthcare products Regulatory Agency, or MHRA, or other regulatory agencies to perform studies and trials in addition to those that we currently anticipate.

Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product on our own. Even if we were able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

We will require additional financial resources to continue as a going concern and to continue ongoing development of our product candidates and pursue our business objectives; if we are unable to obtain these additional resources when needed or on acceptable terms, we may be forced to delay or discontinue our planned operations, including clinical testing of our product candidates.

We have used substantial funds to develop our RNAi technologies and will require substantial funds to conduct further research and development, including preclinical testing and clinical trials of our product candidates, and to manufacture, market and sell any of our products that may be approved for commercial sale. Because the length of time or activities associated with successful development of our product candidates may be greater than we anticipate, we are unable to estimate the actual funds we will require to develop and commercialize them. As of December 31, 2022, our accumulated losses since inception were £263.3 million. We expect our operating expenditures and net losses to increase significantly in connection with our ongoing clinical trials and our internal research and development capabilities.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. We expect our research and development expenses to substantially increase in connection with our ongoing activities, particularly as we advance our product candidates towards or through clinical trials. We will need additional capital to fund our operations and such funding may not be available to us on acceptable terms, or at all. We may need additional capital or to otherwise obtain funding through additional strategic collaborations if we choose to initiate clinical trials for product candidates other than those which are funded by our collaboration partners. In any event, we will require additional capital to obtain regulatory approval for, and to commercialize, future product candidates.

For the foreseeable future, we expect to rely primarily on additional non-dilutive collaboration arrangements, as well as equity and/or debt financings, to fund our operations. Raising additional capital through the sale of securities could cause significant dilution to our shareholders. Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. Our ability to raise additional funds will depend, in part, on the success of our preclinical studies and clinical trials and other product development activities, regulatory events, our ability to identify and enter into licensing or other strategic arrangements, and other events or conditions that may affect our value or prospects, as well as factors related to financial, economic and market conditions, many of which are beyond our control. There can be no assurances that sufficient funds will be available to us when required or on acceptable terms, if at all. If we are unable to raise additional capital when required or on acceptable terms, we may be required to:

- significantly delay, scale back or discontinue the development or commercialization of any future product candidates;
- seek strategic alliances for research and development programs at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available;
- dispose of technology assets, or relinquish or license on unfavorable terms, our rights to technologies or any future product candidates that we otherwise would seek to develop or commercialize; and
- file for bankruptcy or cease operations altogether.

Any of these events would have a material adverse effect on our business, operating results and prospects and could significantly impair the value of your investment in our ADSs.

The Company has incurred recurring losses since inception, including net losses of £40.5 million for the year ended December 31, 2022. As of December 31, 2022, the Company had accumulated losses of £263.3 million and cash outflows from operating activities for the year ended 31 December 2022 of £45.5 million. The Company expects to incur operating losses for the foreseeable future as it continues its research and development efforts, seeks to obtain regulatory approval of its product candidates and pursues any future product candidates the Company may develop.

To-date, the Company has funded its operations through upfront payments and milestones from collaboration agreements, equity offerings and proceeds from private placements, as well as management of expenses and other financing options to support its continued operations. During 2021, the Company received \$40.0 million (£30.8 million) of the upfront payments in respect of the AstraZeneca collaboration, \$45 million from a private placement of ADSs (approximately \$42.0 million / £30.8 million, net of expenses) and approximately \$16.0 million (£10.7 million)

of the upfront payment, (net of taxes withheld, based on the exchange rate at the payment date), related to the Hansoh Pharmaceutical Group Company Limited or Hansoh, collaboration executed on October 14, 2021. In August 2022 the Company raised additional funds through a registered direct offering with aggregate gross proceeds of \$56.5 million (approximately £46.4 million) before deducting \$4.1 million (approximately £3.3 million) in underwriting discounts, commissions and estimated offering expenses. As of December 31, 2022, the Company had cash and cash equivalents and U.S Treasury Bills of £71.1 million (\$86.0 million).

The Company has the responsibility to evaluate whether conditions and/or events raise material uncertainty about its ability to meet its future financial obligations as they become due within one year after the date that the financial statements are issued. The forecast for evaluating the going concern basis of the Company includes continued investment in our technology platform and product pipeline. The forecast does not include collaboration milestones which have not been fully achieved or other assumptions for potential future non-dilutive or dilutive funding sources. Based on this evaluation, the Company believes that its current cash and cash equivalents are only sufficient to fund its operating expenses through the first quarter of 2024. This indicates that a material uncertainty exists that may cast significant doubt (or raise substantial doubt as contemplated by Public Company Accounting Oversight Board ("PCAOB") standards) on the Company's ability to continue as a going concern and therefore the Company may be unable to realize assets and discharge liabilities in the normal course of business.

The Company will need to raise additional funding to fund its operation expenses and capital expenditure requirements in relation to its clinical development activities. The Company may seek additional funding through public or private financings, debt financing or collaboration agreements. Specifically, the Company may receive future milestone payments of up to \$14 million from existing collaboration agreements in the next 12 months which will extend the ability to fund operations beyond the first quarter of 2024. However, these future milestone payments are dependent on achievement of certain development or regulatory objectives that may not occur. The Company has an authorized open market sale agreement and can potentially raise funds through the sale of ADSs. However, there is no assurance that we will be successful in obtaining sufficient funding on terms acceptable to us, or if at all. The inability to obtain future funding could impact; the Company's financial condition and ability to pursue its business strategies, including being required to delay, reduce or eliminate some of its research and development programs, or being unable to continue operations or unable to continue as a going concern.

These consolidated financial statements have been prepared assuming that the Company will continue as a going concern which contemplates the continuity of operations, realization of assets and the satisfaction of liabilities in the ordinary course of business and do not include adjustments that would result if the Company were unable to continue as a going concern.

The forecast of cash resources is forward-looking information that involves risks and uncertainties, and our actual cash requirements may vary materially from our current expectations for a number of other factors that may include, but are not limited to, changes in the focus and direction of our development programs, slower and/or faster than expected progress of our research and development efforts, changes in governmental regulation, competitive and technical advances, rising costs associated with the development of our product candidates, our ability to secure partnering arrangements, and costs of filing, prosecuting, defending and enforcing our intellectual property rights. Global political and economic events, including the COVID-19 pandemic and increased inflation, have already resulted in a significant disruption of global financial markets. If the disruption persists and deepens, we could experience an inability to access additional capital or make the terms of any available financing less attractive, which could in the future negatively affect our operations. If we exhaust our capital reserves more quickly than anticipated, regardless of the reason, and we are unable to obtain additional financing on terms acceptable to us or at all, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Raising additional capital may cause dilution to our holders, including holders of our ADSs, restrict our operations or require us to relinquish rights to our technologies or product candidates.

We expect that additional capital will be needed in the future to continue our planned operations, including expanded research and development activities and potential commercialization efforts. Until such time, if ever, as we

can generate substantial product revenues, we expect to finance our cash needs through any or a combination of securities offerings, debt financings, license and collaboration agreements and research grants and tax credits.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, including in any at-the-market offering through our open market sale agreement, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a shareholder. Debt financing and preferred equity financing, if available, could result in fixed payment obligations, and we may be required to accept terms that restrict our ability to incur additional indebtedness, force us to maintain specified liquidity or other ratios or restrict our ability to pay dividends or make acquisitions. If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. In addition, we could also be required to seek funds through arrangements with collaborators or others at an earlier stage than otherwise would be desirable.

If we raise funds through research grants or take advantage of research and development tax credits, we may be subject to certain requirements, which may limit our ability to use the funds or require us to share information from our research and development. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to a third party to develop and market product candidates that we would otherwise prefer to develop and market ourselves. Raising additional capital through any of these or other means could adversely affect our business and the holdings or rights of our shareholders, and may cause the market price of our ADSs to decline.

Risks Related to the Discovery, Development, Regulatory Approval and Potential Commercialization of Our Product Candidates

The approach we are taking to discover and develop drugs is novel and may never lead to marketable products.

We have concentrated our therapeutic product research and development efforts on siRNA technology, and our future success depends on the successful development of this technology and products based on our siRNA product platform. Although the FDA has approved five siRNA treatments for marketing in the United States since 2018, no assurance can be given that the FDA will approve any other siRNA treatments such as ours.

The scientific discoveries that form the basis for our efforts to discover and develop product candidates based on siRNA technology are relatively new. The scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. If we do not successfully develop and commercialize product candidates based upon our technological approach, we may not become profitable and the value of our ordinary shares may decline.

Further, our focus solely on siRNA technology for developing drugs as opposed to multiple, more proven technologies for drug development increases the risks associated with the ownership of our ordinary shares. If we are not successful in developing any product candidates using siRNA technology, we may be required to change the scope and direction of our product development activities. In that case, we may not be able to identify and successfully implement an alternative product development strategy.

We may not be successful in our efforts to identify or discover potential product candidates.

The success of our business depends primarily upon our ability to identify, develop and commercialize siRNA therapeutics. Our research programs may show initial promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- our research methodology or that of any strategic collaborator may be unsuccessful in identifying potential product candidates that are successful in clinical development;
- 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 receive marketing approval;

- our current or future strategic collaborators may change their development profiles for potential product candidates or abandon a therapeutic area; or
- new competitive developments in the evolving field of RNAi, including gene therapy or gene editing, may render our product candidates obsolete or noncompetitive.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful.

We may not be successful in our efforts to increase our pipeline, including by pursuing additional indications for our current product candidates, identifying additional indications for our proprietary platform technology or in-licensing or acquiring additional product candidates for other indications.

We may not be able to develop or identify product candidates that are safe, tolerable and effective. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify, in-license or acquire may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance.

Preclinical studies and clinical trials of our product candidates may not be successful. If we are unable to generate successful results from these studies and trials, or experience significant delays in doing so, our business may be materially harmed.

We have invested a significant portion of our efforts and financial resources in the identification and development of siRNA-based product candidates. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates.

The success of our product candidates will depend on several factors, including, *inter alia*, the following:

1. successfully designing preclinical studies which may be predictive of clinical outcomes;
2. successfully conducting and completing clinical trials;
3. obtaining and maintaining marketing approvals from applicable regulatory authorities;
4. obtaining and maintaining patent or trade secret protection for future product candidates;
5. establishing and maintaining supply and manufacturing relationships with third parties or establishing our own manufacturing capability; and
6. successfully commercializing our products, if and when approved, whether alone or in collaboration with others.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully complete the development of, or commercialize, our product candidates, which would materially harm our business.

If clinical trials of our product candidates fail to commence or, once commenced fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities, or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

In clinical development, the risk of failure for product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. We are the sponsor of Investigational Medicinal Product Dossiers in multiple jurisdictions and must achieve and maintain compliance with the requirements of various regulatory authorities. Before obtaining marketing approval from regulatory authorities for the sale of product candidates, we or a strategic collaborator must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. As of the date hereof, we have three product candidates in clinical development, and our other product candidates are preclinical. Clinical trials are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. The outcome of early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Moreover, clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in clinical trials have nonetheless failed to obtain marketing approval for their products.

Events which may result in a delay or unsuccessful completion of clinical development include, among other things:

- delays in reaching an agreement with the FDA, EMA, MHRA or other regulatory authorities on final trial design;
- imposition of a clinical hold on our clinical trial operations or trial sites by the FDA or other regulatory authorities;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- inability to adhere to clinical trial requirements directly or with third parties such as CROs;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical trial site;
- delays in recruiting suitable patients to participate in a trial;
- delays in the testing, validation, manufacturing and delivery of the product candidates to the clinical sites;
- delays in having patients complete participation in a trial or return for post-treatment follow-up;
- delays caused by patients dropping out of a trial due to protocol procedures or requirements, product side effects or disease progression;
- clinical sites dropping out of a trial to the detriment of enrollment;
- time required to add new clinical sites;
- negative outcomes, including deficiencies in good clinical practices, or GCP, in routine inspections by regulatory authorities in the countries where our clinical trials are being conducted;
- investigator fraud, including data fabrication by clinical trial personnel;
- delays by our contract manufacturers to produce and deliver sufficient supply of clinical trial materials; or
- delays in delivering sufficient supply of clinical trial materials to clinical sites and challenges in patient recruitment, including due to the COVID-19 pandemic, as well as challenges regarding global clinical trial supply shipments, importation and customs clearances.

If we or our current or future strategic collaborators are required to conduct additional clinical trials or other testing of any product candidates beyond those that are currently contemplated, are unable to successfully complete clinical trials of any such product candidates or other testing, or if the results of these trials or tests are not positive or are only moderately positive, or if there are safety concerns, we and they may:

- be delayed in obtaining marketing approval for our future product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as originally intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

Many 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. In addition, our product development costs will also increase if we experience delays in testing or marketing approvals. We do not know whether any clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which would impair our ability to successfully commercialize our product candidates and may harm our business and results of operations. Any inability to successfully complete clinical development, whether independently or with a strategic collaborator, could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestone payments and royalties.

Conducting successful clinical trials requires the enrollment of large numbers of patients, and suitable patients may be difficult to identify and recruit.

Patient enrollment in clinical trials and completion of patient participation and follow-up depends on many factors, including the size of the patient population; the nature of the trial protocol; the attractiveness of, or the discomforts and risks associated with, the treatments received by enrolled subjects; the availability of appropriate clinical trial investigators; support staff; the number of ongoing clinical trials in the same indication that compete for the same patients; proximity of patients to clinical sites and ability to comply with the eligibility and exclusion criteria for participation in the clinical trial and patient compliance. For example, patients may be discouraged from enrolling in our clinical trials if the trial protocol requires them to undergo extensive post-treatment procedures or follow-up to assess the safety and effectiveness of our products or if they determine that the treatments received under the trial protocols are not attractive or involve unacceptable risks or discomforts. Patients may also not participate in our clinical trials if they choose to participate in contemporaneous clinical trials of competitive products.

We rely on third parties to conduct some aspects of our manufacturing, research and development activities, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of research or clinical testing, or may terminate our agreements.

We do not expect to independently conduct all aspects of our manufacturing and drug discovery activities, research or preclinical and clinical studies of product candidates. We currently rely and expect to continue to rely on third parties to conduct some aspects of our drug development studies and chemical syntheses. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the necessary preclinical studies to enable us to progress viable product candidates for

investigational new drug, or IND, submissions and will not be able to, or may be delayed in our efforts to, successfully develop and commercialize such product candidates.

Although our research and development services can only be performed by us or at our discretion, we rely on third party clinical investigators, CROs, clinical data management organizations, medical institutions and consultants to design, conduct, supervise and monitor preclinical studies and clinical trials in relation to our product candidates. Because we rely on third parties and do not have the ability to conduct clinical trials independently, we have less control over the timing, quality and other aspects of clinical trials than we would if we conducted them on our own. These investigators, CROs and consultants are not our employees and we have limited control over the amount of time and resources that they dedicate to our programs. These third parties may have contractual relationships with other entities, some of which may be our competitors, which may draw time and resources from our programs. If we cannot contract with acceptable third parties on commercially reasonable terms, or at all, or if these third parties do not carry out their contractual duties, satisfy legal and regulatory requirements for the conduct of clinical trials or meet expected deadlines, our clinical development program could be delayed or otherwise adversely affected. In all events, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. The FDA and comparable foreign regulatory agencies require us to comply with GCP for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible, accurate and complete and that the rights, integrity and confidentiality of trial participants are protected. We rely, for example, on third parties for aspects of quality control which are especially important in monitoring compliance with GCP requirements and avoiding any investigator fraud or misconduct in clinical research, such as practices including adherence to an investigational plan; accurate recordkeeping; drug accountability; obtaining completed informed consent forms; timely reporting of any adverse drug reactions; notifying appropriate IRBs and Ethics Committees of progress reports and any significant changes; and obtaining documented IRB approvals. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. The third parties with which we contract might not be diligent, careful or timely in conducting our clinical trials, as a result of which we could experience one or more lapses in quality controls or other aspects of clinical trial management, and the clinical trials could be delayed or unsuccessful. Any such event could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our dependence on collaborators for capabilities and funding means that our business could be adversely affected if any collaborator materially amends or terminates its collaboration agreement with us or fails to perform its obligations under that agreement. Our current or future collaborations, if any, may not be scientifically or commercially successful. Disputes may arise in the future with respect to the ownership of rights to technology or products developed with collaborators, which could have an adverse effect on our ability to develop and commercialize any affected product candidate. Our current collaborations allow, and we expect that any future collaborations will allow, either party to terminate the collaboration for a material breach by the other party. In addition, our collaborators may have additional termination rights for convenience with respect to the collaboration or a particular program under the collaboration, under certain circumstances. For example, our collaboration agreement with Mallinckrodt plc, or Mallinckrodt, for an exclusive worldwide license for SLN501 (SLN500 program candidate) and additional complement-target products, our collaboration agreement with AstraZeneca PLC, or AstraZeneca, to discover, develop and commercialize siRNA therapeutics for the treatment of cardiovascular, renal, metabolic and respiratory diseases, and our collaboration agreement with Hansoh Pharmaceutical Group Company Limited, or Hansoh, to develop siRNAs for three undisclosed targets, may be terminated by Mallinckrodt, AstraZeneca and Hansoh, respectively, at any time upon prior written notice to us. If we were to lose a collaborator, we would have to attract a new collaborator or develop expanded R&D, sales, distribution and marketing capabilities internally, which would require us to invest significant amounts of financial and management resources.

We rely on third-party manufacturers to produce our preclinical, clinical product candidates and certain starting material components, and we intend to rely on third parties to produce future clinical supplies of product candidates that we advance into clinical trials and commercial supplies of any approved product candidates.

Reliance on third-party manufacturers entails risks, including risks that we would not be subject to if we manufactured the product candidates ourselves, including:

- the inability to meet any product specifications and quality requirements consistently;

- a delay or inability to procure or expand sufficient manufacturing capacity;
- manufacturing and product quality issues related to scale-up of manufacturing;
- costs and validation of new equipment and facilities required for scale-up;
- a failure to comply with applicable government regulations;
- the inability to negotiate manufacturing or supply agreements with third parties under commercially reasonable terms or at all;
- termination or non-renewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- the reliance on a limited number of sources, such that if we were unable to secure a sufficient supply of these product components, we will be unable to manufacture and sell future product candidates in a timely fashion, in sufficient quantities or under acceptable terms; and
- the losses incurred by us if our insurance coverage is insufficient to cover any loss, contamination or damage of chemical materials, product components or products made by any of our CMOs, once the materials or products have been shipped to us and the risk of loss has been transferred to us.

We face risks inherent in relying on contract manufacturing organizations, or CMOs, as any disruption, such as a fire, natural hazards, pandemic, epidemic, war or outbreak of an infectious disease at a CMO could significantly interrupt our manufacturing capability. If necessary to avoid future disruption, we may have to establish alternative manufacturing sources. This would require substantial capital on our part, which we may not be able to obtain on commercially acceptable terms or at all. Additionally, we may experience manufacturing delays as we build or locate replacement facilities and seek and obtain necessary regulatory approvals. If this occurs, we will be unable to satisfy manufacturing needs on a timely basis, if at all. Also, operating any new facilities may be more expensive than operating our current facility. Further, business interruption insurance may not adequately compensate us for any losses that may occur and we would have to bear the additional cost of any disruption. For these reasons, a significant disruptive event affecting the manufacturing facility could have drastic consequences, including placing our financial stability at risk.

Even if we complete the necessary preclinical studies and clinical trials, we cannot predict whether or when we will obtain regulatory approval to commercialize a product candidate and we cannot, therefore, predict the timing of any revenue from a future product.

Neither we nor any strategic collaborator can commercialize a product until the appropriate regulatory authorities, such as the FDA, EMA or MHRA, have reviewed and approved the product candidate. The regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee, or similar foreign governmental institution, recommends restrictions or conditions on approval or recommends non-approval. In addition, we or a strategic collaborator may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process.

Even if we obtain regulatory approval for a product candidate, we will still face extensive regulatory requirements and our products may face future development and regulatory difficulties.

Even if we obtain regulatory approval in the United States and the European Union, the FDA and the EMA may still impose significant restrictions on the indicated uses or marketing of our product candidates or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance. The holder of an approved new drug application, or NDA, in the United States, or a marketing authorization, or MA, in the European Union is obligated to monitor and report adverse events, or AEs, or adverse reactions and any failure of a product to meet the

specifications in the NDA, or MA. The holder of an approved NDA or MA must also submit new or supplemental applications and obtain regulatory approval in order to make certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with the relevant regulatory rules and, in the United States and in some EU Member States, are subject to FDA review or national regulatory review, in addition to other potentially applicable federal and state laws.

In addition, drug product manufacturers and their facilities are subject to payment of user fees or may require manufacturing and import authorizations, or MIAs in the European Union, and continual review and periodic inspections by regulatory authorities for compliance with current good manufacturing practices, or cGMP, including quality control, quality assurance, and the maintenance of records and documentation to ensure that approved products are safe and consistently meet applicable requirements, and adherence to commitments made in the NDA or MA. While we have not yet, and may not ever, obtain marketing approval for any of our products, when we do, we or any third party manufacturers we engage may be unable to comply with these cGMP and with other regulatory authority requirements. These requirements are enforced by regulatory authorities through periodic inspections of manufacturing facilities. If we or a regulatory agency discovers previously unknown problems with a product such as AEs of unanticipated severity or frequency, adverse reactions, or product quality issues, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions relative to that product or the manufacturing facility. A negative outcome from such inspection or a failure to provide adequate and timely corrective actions in response to deficiencies identified could result in enforcement action, including warning letters, fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, plant shutdown, or the delay, withholding, or withdrawal of product approval. If the safety of any product is compromised due to a manufacturer's failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our products, which would seriously harm our business.

If there are changes in the application of legislation or regulatory policies, or if problems are discovered with a product or our manufacture of a product, or if we or one of our distributors, licensees or co-marketers fails to comply with regulatory requirements, the regulators could take various actions such as:

- issuing a warning letter or untitled letter asserting that we are in violation of the law;
- seeking an injunction or imposing civil or criminal penalties or monetary fines;
- suspending or withdrawing regulatory approval;
- suspending any ongoing clinical trials;
- refusing to approve a pending NDA or MA or supplements to an NDA or MA submitted by us;
- seizing product; or
- refusing to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our future products and generate revenues.

Even if we obtain and maintain approval for our product candidates in one jurisdiction, we may never obtain approval for our product candidates with other regulatory authorities in other jurisdictions. Sales of our product candidates outside of the United States and the European Union will be subject to foreign regulatory requirements governing clinical trials and marketing approval and continual regulatory review. We will be subject to ongoing obligations and oversight by regulatory authorities, including adverse event reporting requirements, marketing restrictions and, potentially, other post-marketing obligations, all of which may result in significant expense and limit our ability to commercialize such products.

We may not be able to obtain or maintain orphan drug designations for any of our product candidates, and we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs or biologics for relatively small patient populations as orphan drugs. In the United States, under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition. Such diseases and conditions are those that affect fewer than 200,000 individuals in the United States, or if they affect more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making a drug available in the United States for these types of diseases or conditions will be recovered from sales of the drug. However, orphan drug designation must be requested before submitting an NDA and there can be no assurance that any such designation will be granted. If the FDA grants orphan drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

In the United States, orphan drug designation recipients can take advantage of special incentives provided by the FDA such as (i) potential market exclusivity of the product for seven years as the first sponsor (ii) tax credits for qualified clinical research for a designated orphan product and (iii) waiver of associated fees when submitting a marketing application to the FDA.

Similarly, in the European Union, orphan designation is intended to promote the development of medicinal products that are intended for (i) the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union, or that are intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition when, without incentives, it is unlikely that sales in Europe would be sufficient to justify the necessary investment, and (ii) there exists no satisfactory method of diagnosis, prevention or treatment of the condition that has been authorized in Europe or, if such method exists, that the medicinal product will be of significant benefit to those affected. In Europe, orphan designation entitles a party to a number of incentives, such as protocol assistance and scientific advice specifically for designated orphan medicines, and potential fee reductions depending on the status of the sponsor. European orphan medicines also benefit from ten years of market exclusivity, which precludes the EMA from approving another marketing application during this time period for a similar drug and for the same indication. This marketing exclusivity period can however, be reduced to six years if, at the time the marketing authorization is renewed after five years, a drug no longer meets the criteria for orphan designation or if the drug is sufficiently profitable, such that market exclusivity is no longer justified.

Our product candidate SLN124 has received orphan drug designation from the EMA for the treatment of beta-thalassemia and from the FDA for the treatment of beta-thalassemia, myelodysplastic syndrome, or MDS, and polycythemia vera, or PV. Our drug candidate SLN501 (collaboration with Mallinckrodt) has received orphan drug designation from the FDA for complement 3 glomerulopathy, or C3G. The EMA will reassess eligibility for SLN124 orphan exclusivity at the time of MA review and can remove orphan status if the drug no longer meets the eligibility criteria, including offering a significant benefit to those affected, at that time. Moreover, even if we obtain orphan drug exclusivity in the future for a product candidate for these or other indications, such exclusivity may not effectively protect the product candidate from competition because different therapies can be approved for the same condition and the same therapies can be approved for different conditions but used off-label. Even after an orphan drug is approved, the FDA or EMA can subsequently approve a different or a similar drug for the same condition if such regulatory authority concludes that the later drug is clinically superior because it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity may also be lost if the regulatory authority later determines that the initial request for designation was materially defective. In addition, orphan drug exclusivity does not prevent the regulatory authority from approving competing drugs for the same disease or condition containing a different active ingredient. In addition, if a subsequent drug is approved for marketing for the same disease or condition as any of our product candidates that receive marketing approval, we may face increased competition and lose market share regardless of orphan drug exclusivity.

Although we have obtained Rare Pediatric Disease Designation for SLN124 for the treatment of beta-thalassemia, we may not realize the expected benefits of this designation.

In 2012, Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications. This provision is designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases. Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. The FDA may also revoke any priority review voucher if the rare pediatric disease drug for which the voucher was awarded is not marketed in the U.S. within one year following the date of approval.

SLN124 has been granted rare pediatric disease designation, but designation of a drug for a rare pediatric disease does not guarantee that an NDA will meet the eligibility criteria for a rare pediatric disease priority review voucher at the time the application is approved. Specifically, on December 27, 2020, the Rare Pediatric Disease Priority Review Voucher Program was extended by Congress; under the current statutory sunset provisions, after September 30, 2024, FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024. After September 30, 2026, FDA may not award any rare pediatric disease priority review vouchers. Furthermore, a Rare Pediatric Disease Designation does not lead to faster development or regulatory review of the product, or increase the likelihood that it will receive marketing approval. We may or may not realize any benefit from receiving a voucher.

We may use our financial and human resources to pursue a particular research program or product candidate and fail to capitalize on programs or product candidates that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and human resources, we intend to leverage our existing licensing and collaboration agreements and may enter into new strategic collaboration agreements for the development and commercialization of our programs and potential product candidates in indications with potentially large commercial markets while focusing our internal development resources, and any future internal sales and marketing organization that we may establish, on research programs and product candidates intended for selected markets or patient populations, such as rare diseases. As a result, and even as we prioritize rare indications with expansion opportunities to large populations, we may forego or delay pursuit of other programs or product candidates or other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a collaboration arrangement.

Any of our product candidates may cause adverse effects or have other properties that could delay or prevent their regulatory approval or limit the scope of any approved label or market acceptance.

AEs caused by our product candidates could cause us, other reviewing entities, clinical trial sites or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval. Certain oligonucleotide therapeutics have been observed to result in injection site reactions and pro-inflammatory effects and may also lead to impairment of kidney or liver function. There is a risk that our future product candidates may induce similar AEs.

If AEs are observed in any clinical trials of our product candidates, including those that a strategic collaborator may develop under an agreement with us, our or our collaborators' ability to obtain regulatory approval for product candidates may be negatively impacted.

Further, if any of our future products, if and when approved for commercial sale, cause serious or unexpected side effects, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw their approval of the product or impose restrictions on our distribution in the form of a risk evaluation and mitigation strategy;
- regulatory authorities may require the addition of labeling statements, such as warnings or contraindications;
- we may be required to change the way the product is administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; or
- our reputation may suffer.

Any of these events could prevent us or our collaborators from achieving or maintaining market acceptance of the affected product and could substantially increase the costs of commercializing our future products and impair our ability to generate revenues from the commercialization of these products either on our own or with the collaborator.

Even if any of our product candidates receive marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, third party payers and others in the medical community necessary for commercial success.

The product candidates that we are developing are based upon new technologies or therapeutic approaches. Key participants in pharmaceutical marketplaces, such as physicians, third-party payers and consumers, may not accept a product intended to improve therapeutic results based on RNAi technology. As a result, it may be more difficult for us to convince the medical community and third-party payers to accept and use our product, or to provide favorable reimbursement and market access. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy, safety and potential advantages of any of our product candidates compared to alternative treatments;
- our ability to offer our products for sale at competitive prices;
- the stability, shelf life, convenience and ease of storage and administration compared to alternative treatments;
- the willingness of the target patient population to try new treatments and of physicians to prescribe these treatments;
- our ability to hire and retain a sales force, or to engage one or more third party distributors for our products;
- the strength of marketing and distribution support;
- the availability of third party payer coverage and adequate reimbursement for our product candidates;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our products together with other medications.

Risks Related to Our Business Operations and Compliance with Government Regulations

We face competition from other companies that are working to develop novel drugs and technology platforms using technologies similar to ours. If these companies develop drugs more rapidly than we do or their technologies, including delivery technologies, are more effective, our ability to successfully commercialize drugs may be adversely affected.

We face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions. Many of our competitors may have greater experience in research and development, manufacturing, managing clinical trials and/or regulatory compliance than we do, and may be better resourced financially. Any product candidates that we successfully develop and commercialize will compete with existing products and new products that may become available in the future. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and recruiting lead clinical trial investigators and establishing clinical study sites and patient registration for clinical studies, as well as in acquiring technologies complementary to, or necessary for, our programs.

Companies that complete clinical trials, obtain required regulatory authority approvals and commence commercial sale of their drugs before we do may achieve a significant competitive advantage, and our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop and commercialize. Because our products and many potential competing products are in various stages of preclinical and clinical development, and given the inherent unpredictability of drug development, it is difficult to predict which third parties may provide the most competition, and on what specific basis.

In addition to the competition we face from competing drugs in general, we also face competition from other companies working to develop novel drugs using technology that competes more directly with our own. We are aware of several other companies that are working to develop RNAi therapeutic products and other companies may develop alternative treatments for the diseases we have identified as being potentially treated with our siRNA molecules. To the extent those alternative treatments are more efficacious, less expensive, more convenient or produce fewer side effects, our market opportunity would be reduced.

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. Certain of our executive officers are “at will” employees and may terminate their employment with us at any time upon prior written notice. Recruiting and retaining other qualified employees for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous life sciences companies for individuals with similar skill sets. In addition, failure to succeed in preclinical studies and clinical trials may make it more challenging to recruit and retain qualified personnel.

The inability to recruit or loss of the services of any executive or key employee might impede the progress of our research, development and commercialization objectives.

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

As of December 31, 2022 we had 122 employees. In the future we may expand our employee base to increase our managerial, scientific, operational, commercial, financial and other resources and to hire more consultants and contractors. Future growth would impose significant additional responsibilities on our management, including the need to identify, recruit, maintain, motivate and integrate additional employees, consultants and contractors. Also, our

management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. Moreover, if our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

If we fail to introduce new products or keep pace with advances in technology, our business, financial condition and results of operations could be adversely affected.

We spend a relatively low amount on technological innovation compared to our larger competitors. There is a risk that competitors will be quicker to develop new technologies, new products for the same gene targets or new delivery methods of nucleic acids into novel cell types, particularly once competitors learn about new gene targets that we or our collaborators have selected for development of siRNA molecules. We will need to successfully introduce new products to achieve our strategic business objectives. Our successful product development will depend on many factors, including our ability to attract strong talent to lead our research and development efforts, adapt to new technologies, obtain regulatory approvals on a timely basis, demonstrate satisfactory clinical results, manufacture products in an economical and timely manner, obtain appropriate intellectual property protection for our products, gain and maintain market acceptance of our products, and differentiate our products from those of our competitors. In addition, patents attained by others may preclude or delay our commercialization of a product. There can be no assurance that any products now in development or that we may seek to develop in the future will achieve technological feasibility, obtain regulatory approval or gain market acceptance. If we cannot successfully introduce new products or adapt to changing technologies, our products may become obsolete and our revenue and profitability could suffer.

We face potential product liability and other claims, and, if successful claims are brought against us, we may incur substantial liability and costs.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims, including claims related to impurities in our products or potential product recalls. Certain single-stranded oligonucleotide therapeutics have led to injection site reactions and pro-inflammatory effects and may also lead to impairment of kidney or liver function. There is a risk that our current and future product candidates, although double-stranded, may induce similar or other adverse events. Product liability claims might be brought against us by consumers, healthcare providers, life sciences companies or others selling or otherwise coming into contact with our products; other claims may be brought against us by third parties with whom we contract, or by current or former employees or consultants, including claims of wrongful terminations, discrimination, other violations of labor law or other alleged conduct. If we cannot successfully defend against such claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, such claims may result in, among other things:

- impairment of our business reputation;
- withdrawal of clinical trial participants with respect to product liability claims;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to claimants;
- the inability to commercialize our product candidates; and

- decreased demand for our product candidates, if approved for commercial sale.

We maintain product liability insurance relating to the use of our therapeutics in clinical trials. However, such insurance coverage may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and in the future we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Cybersecurity risks and the failure to maintain the confidentiality, integrity, and availability of our computer hardware, software, and internet applications and related tools and functions could result in damage to our reputation and/or subject us to costs, fines or lawsuits.

Our business requires manipulating, analyzing and storing large amounts of data. We also maintain personally identifiable information about our employees. Our business therefore depends on the continuous, effective, reliable, and secure operation of our computer hardware, software, networks, internet servers, third party technology service providers and related infrastructure. To the extent that our hardware or software malfunctions or access to our data by internal research personnel is interrupted, our business could suffer. The integrity and protection of our employee and company data is critical to our business and employees have a high expectation that we will adequately protect their personal information. The regulatory environment governing information, security and privacy laws is increasingly demanding and continues to evolve, as further described below. Maintaining compliance with applicable security and privacy regulations may increase our operating costs. Although our computer and communications hardware are protected through physical and software safeguards, we are still vulnerable to fire, storm, flood, power loss, earthquakes, telecommunications failures, physical or software break-ins, software viruses, accidental or malicious insider-action and similar events. These events could lead to the unauthorized access, disclosure and use of non-public information. The techniques used by criminal elements to attack computer systems are sophisticated, change frequently and may originate from less regulated and remote areas of the world and increasingly involve highly resourced threat actors such as organized criminals and nation states. As a result, we cannot provide assurance that our efforts to address these techniques proactively or implement adequate preventative measures will always be successful. If our computer systems are compromised, we could be subject to fines, damages, litigation and enforcement actions, and we could lose trade secrets, the occurrence of which could harm our business. In addition, any sustained disruption in internet systems or network access provided by other companies could harm our business.

The collection, processing and cross-border transfer of personal information is subject to restrictive laws and regulations.

We are subject to privacy and data protection laws and regulations that apply to the collection, transmission, storage and use of personally identifiable information. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing amount of focus on compliance in this area, with the potential to affect our business.

In the European Union and the United Kingdom, the collection and use of personal data (including health data) is governed by the provisions of the EU and U.K. General Data Protection Regulations, or collectively, the GDPR. The GDPR applies to the processing of personal data (i) by businesses established in the European Union or the United Kingdom, regardless of whether the processing takes place in the European Union or the United Kingdom, or (ii) of individuals located in the European Union or the United Kingdom, by businesses established outside of the European Union or the United Kingdom, where they process personal data to (a) offer goods or services to individuals in the European Union or the United Kingdom, or (b) monitor their behavior, as it takes place in the European Union or the United Kingdom (e.g., carrying out clinical trial activities in the European Union or the United Kingdom).

The GDPR imposes data protection obligations on organizations processing personal data, including:

- disclosures to individuals, about, among others, how their personal data are processed, and the legal basis for such processing,
- limitations on the retention of personal data,
- mandatory data breach notification requirements in certain circumstances,
- data processing obligations on service providers who process personal data on behalf of other organizations,
- additional conditions when processing “sensitive data” under the GDPR (which includes health and genetic data of individuals located in the European Union or the United Kingdom),
- having security measures in place appropriate to the risk of processing, and
- responding to individuals exercising their data subject rights under the GDPR (i.e., right of access, erasure, rectification, restriction, objection, and data portability).

The GDPR also imposes strict rules on the transfer of personal data out of the European Economic Area, or EEA, or United Kingdom to third countries, including the United States. In order to transfer personal data outside of the EEA/United Kingdom, businesses will need to rely on (i) an adequacy decision (i.e., a finding by the European Commission or the United Kingdom that the destination country offers an “adequate” level of data protection), (ii) an appropriate safeguard (e.g., Standard Contractual Clauses), or (iii) a derogation. Failure to comply with the requirements of the EU’s GDPR may result in fines of up to 4% of an undertaking’s total global annual turnover for the preceding financial year, or €20,000,000, whichever is greater. In addition to administrative fines, a wide variety of other potential enforcement powers are available to data supervisory authorities in respect of potential and suspected violations of the GDPR, including extensive audit and inspection rights, and powers to order temporary or permanent bans on all or some processing of personal data carried out by noncompliant actors. While we have taken steps to comply with the GDPR, and implementing legislation in applicable EU member states and the United Kingdom, including seeking to establish appropriate lawful bases for the various processing activities we carry out as a controller, adopting an international transfer mechanism, where applicable, reviewing our security procedures, and entering into data processing agreements with relevant vendors and business partners, we cannot guarantee that our efforts to achieve and remain in compliance have been, and/or will continue to be, fully successful.

Additionally, the United Kingdom has transposed the GDPR into U.K. domestic law by way of the U.K. GDPR. As a result, we are exposed to two parallel regimes, each with enforcement powers. Failure to comply with the U.K. GDPR may result in fines of up to 4% of total global annual turnover or £17,500,000 for violations of the U.K. GDPR. Also, following the expiry of the post-Brexit transitional arrangements, the U.K. Information Commissioner’s Office cannot be our “lead supervisory authority” in respect of any “cross border processing” for the purposes of the EU’s GDPR. For so long as we are unable to, and/or do not, designate a lead supervisory authority in an EEA member state, we are not able to benefit from the GDPR’s “one stop shop” mechanism. Among other things, this would mean that, in the event of a violation of the GDPR affecting data subjects across the United Kingdom and the EEA, we could be investigated by, and ultimately fined by the U.K. Information Commissioner’s Office and the supervisory authority in each and every EEA member state where data subjects have been affected by such violation. Other countries have also passed or are considering passing laws requiring local data residency and/or restricting the international transfer of data.

Similarly, failure to comply with federal and state laws in the United States regarding privacy and security of personal information could further expose us to penalties under privacy and data protection laws. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our business.

Our employees, consultants and contractors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements or insider trading violations, which could significantly harm our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees, consultants or contractors could include intentional failures to comply with governmental regulations, comply with healthcare fraud and abuse and anti-kickback laws and regulations in the United States, the United Kingdom and other jurisdictions, or failure to 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. Employee misconduct could also involve the improper use of, including improper trading based upon, information obtained in the course of clinical studies, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a code of business conduct and ethics and a robust compliance program, but it is not always possible to identify and deter employee misconduct, and the 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 have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Healthcare legislative reform measures may have a negative impact on our business and results of operations.

In the United States, there have been, and continue to be, legislative and regulatory developments regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities, and affect our ability to profitably sell any product candidates for which we obtain marketing approval. Additionally, 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. Such scrutiny has resulted in several recent 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 products. While any proposed measures will require authorization through additional legislation to become effective, Congress and the current administration have each indicated that they will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological 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. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or successfully commercialize our drugs.

The withdrawal of the United Kingdom from the European Union, commonly referred to as “Brexit,” may adversely impact our ability to obtain regulatory approvals of our product candidates in the European Union, result in restrictions or imposition of taxes and duties for importing our product candidates into the European Union, may require additional licenses and procedural steps and may require us to incur additional expenses in order to develop, manufacture and commercialize our product candidates in the European Union.

Following the result of a referendum in 2016, the United Kingdom left the European Union on January 31, 2020, commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the United Kingdom and the EU, the United Kingdom was subject to a transition period until December 31, 2020, or the Transition Period, during which EU rules continued to apply. The Trade and Cooperation Agreement, which outlines the future trading relationship between the United Kingdom and the EU was agreed in December 2020 and entered into force on May 1, 2021.

Since a significant proportion of the regulatory framework in the United Kingdom applicable to our business and our product candidates is derived from EU directives and regulations, Brexit has had, and may continue to have, a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and

commercialization of our product candidates in the United Kingdom or the EU. For example, while Northern Ireland continues to be subject to EU pharmaceutical laws and is covered by centralized authorizations, Great Britain is no longer covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA and a separate marketing authorization will be required to market our product candidates in Great Britain. (referred to as a UKMA(GB)). Therefore, applicants must undergo two separate procedures to obtain marketing authorizations valid in the EU/EEA and Great Britain. The MHRA has established a number of accelerated procedures to allow those applying for a UKMA(GB) to fast-track their application if the applicant has already obtained a marketing authorization(s) through the mutual recognition or decentralized procedure or has a centralized marketing authorization. In these cases the MHRA provides for reliance procedures that allow applicants to obtain a UKMA(GB) within 67 days of marketing authorization validation. However, this procedure can be delayed if there are any major issues (leading to the application being switched to the standard 210-day timetable). Conversely, the EU does not provide for any mutual recognition or reliance routes based on U.K. marketing authorizations. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, could make it more difficult for us to commercialize our product candidates in the European Union or in the United Kingdom and restrict our ability to generate revenue and achieve and sustain profitability. While the Trade and Cooperation Agreement provides for the tariff-free trade of medicinal products between the United Kingdom and the EU, there may be additional non-tariff costs to such trade which did not exist prior to the end of the Transition Period. Although the United Kingdom currently remains aligned with EU pharmaceutical laws, should the United Kingdom diverge from the European Union from a regulatory perspective in relation to medicinal products, additional non-tariff barriers could arise on such trade. We could therefore, both now and in the future, face significant additional expenses (when compared to the position prior to the end of the Transition Period) to operate our business, which could significantly and materially harm or delay our ability to generate revenues or achieve profitability of our business. As Brexit means that the U.K. is a third country, there are also additional requirements around importing and exporting investigational medicinal products, medicinal products and active substances between the U.K and EU that might require additional licenses (e.g. an importation license rather than a wholesale dealers' license) and additional steps (e.g. batch release in the EU).

Additionally, there are potential changes to the regulatory framework in the United Kingdom. Notably, the U.K Government has introduced the Retained EU Law (Revocation and Reform) Bill into Parliament, which proposes that all retained European Union law will expire on December 31, 2023 (or at the latest June 23, 2026), which would include all key pharmaceutical legislative instruments. The Bill proposes to grant certain powers to Government Ministers to make regulations in the affected areas. While the U.K. Government and European Commission have finalized negotiations regarding the terms of the Northern Ireland Protocol, the Windsor Framework will need to be approved in the British Parliament. As such, there could be further uncertainty about the regulatory position in the United Kingdom.

While the Trade and Cooperation Agreement provides for the tariff-free trade of medicinal products between the United Kingdom and the EU, there may be additional non-tariff costs to such trade, which did not exist prior to the end of the Transition Period. Although the United Kingdom currently remains aligned with EU pharmaceutical laws, should the United Kingdom diverge from the European Union from a regulatory perspective in relation to medicinal products, additional non-tariff barriers could arise on such trade. We could therefore, both now and in the future, face significant additional expenses (when compared to the position prior to the end of the Transition Period) to operate our business, which could significantly and materially harm or delay our ability to generate revenues or achieve profitability of our business.

Any further changes in international trade, tariff and import/export regulations as a result of Brexit or otherwise may impose unexpected duty costs or other non-tariff barriers on us. These developments, or the perception that any of them could occur, may significantly reduce global trade and, in particular, trade between the impacted nations and the United Kingdom.

It is also possible that Brexit may negatively affect our ability to attract and retain employees, particularly those from the European Union, and make travel and staff transfers between our United Kingdom and German offices more difficult, time-consuming and expensive than previously was the case.

Legal, political and economic uncertainty surrounding Brexit may be a source of instability in international markets, create significant currency fluctuations, adversely affect our operations in the United Kingdom and pose additional risks to our business, revenue, financial condition, and results of operations.

The lack of clarity on future U.K. laws and regulations, including financial laws and regulations, tax and free trade agreements, intellectual property rights, data protection laws, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, after the expiration of the Transition Period may negatively impact foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict access to capital.

There is a risk that the Windsor Framework will not be approved and that disagreements over the application of a Protocol to the Trade and Cooperation Agreement to Northern Ireland may continue and may lead to the suspension of the Trade and Cooperation Agreement as a whole, or parts thereof. This may lead to new tariffs or non-tariff barriers applying to such trade in the future. The uncertainty concerning the United Kingdom's long-term legal, political and economic relationship with the European Union may be a source of instability in the international markets, create significant currency fluctuations, and/or otherwise adversely affect trading agreements or similar cross-border co-operation arrangements (whether economic, tax, fiscal, legal, regulatory or otherwise). These developments, or the perception that any of them could occur, have had, and may continue to have, a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and limit the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U.K. financial and banking markets, as well as on the regulatory process in Europe. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility.

These developments, or the perception that any of them could occur, have had, and may continue to have, a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and limit the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U.K. financial and banking markets, as well as on the regulatory process in Europe. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility.

If other EU member states pursue withdrawal from the European Union, barrier-free access between the United Kingdom and those EU member states or among countries within the current European Economic Area overall could be diminished or eliminated.

There may continue to be economic uncertainty surrounding the longer-term consequences of Brexit, which could adversely impact third party confidence resulting in collaborators reducing their spending budgets on our product candidates, which could adversely affect our business, revenue, financial condition, results of operations and could adversely affect the market price of our ADSs.

The ongoing effects of the COVID-19 pandemic and post-pandemic effects could adversely affect our clinical trial operations, as well as our supply chain.

Our planned clinical trials may be negatively affected by the COVID-19 pandemic. Clinical site initiation, patient enrollment and first dosing have been delayed due to prioritization of hospital resources toward the COVID-19 pandemic, delays and difficulties in enrolling patients, and staffing issues at clinical trial sites. Our clinical development timelines may be further delayed if our CMOs, CROs and other service providers upon whom we rely experience delays in providing services. Some patients may not be able to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services. We may also experience supply chain constraints as a result of the COVID-19 pandemic, which could impact our ability to conduct clinical trials and develop our products.

While the extent to which the ongoing COVID-19 pandemic impacts our business, our clinical development and regulatory efforts will depend on future developments that are highly uncertain and cannot be predicted with confidence, such as impacts of new variants on the disease, the duration of the outbreak, travel restrictions, quarantines, social distancing requirements, the continued effectiveness of the available vaccines and treatments, the

potential for additional business disruptions and the effectiveness of actions taken in the United States and other countries to continue to manage and treat the disease. Although many states and countries made decisions to relax social distancing requirements and lift travel and other restrictions, local resurgence of COVID-19 infection may occur and could result in prolonged significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity a recession or market correction resulting from the ongoing effects of COVID-19 could materially affect our business and the value of our ADSs. Accordingly, we do not yet know the full extent of potential delays or impacts on our business, our clinical and regulatory activities, healthcare systems or the global economy as a whole. However, these impacts could adversely affect our business, financial condition, results of operations and growth prospects.

In addition, to the extent the ongoing COVID-19 pandemic adversely affects our business and results of operations, it may also have the effect of heightening many of the other risks and uncertainties described in this "Risk Factors" section.

Exchange rate fluctuations may adversely affect our results of operations and cash flows.

Our functional currency is pounds sterling, and our transactions are commonly denominated in that currency. However, we receive payments under our collaboration agreements in U.S. dollars and we incur a portion of our expenses in other currencies, primarily Euros. As a result, fluctuations in exchange rates, particularly between the pound sterling on the one hand and the U.S. dollar and Euro on the other hand, may adversely affect our reported results of operations and cash flows. Our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates between the pound sterling and these and other currencies, any of which may have a significant impact on our results of operations and cash flows from period to period.

If we fail to comply with environmental, 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 are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. 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. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Inflation may adversely affect our operations, including increases in the prices of goods and services required for our operations.

High rates of inflation resulting from global events may adversely affect our operations in the event of increased prices of goods and services, such as energy and other operating costs, labor costs, materials costs and shipping costs, all of which may impact our direct costs. We are also experiencing increases in the cost of services provided by CMOs, CROs and other third parties with whom we do business, including significant increases in the cost of non-human primates required for studies. Such high inflation rates may result in unexpected and unbudgeted cost increases and may require changes to planned investments.

Risks Related to our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our current or future products and product candidates, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our current and future products and product candidates. The strength of patents in the biotechnology and life sciences field involves complex legal and scientific questions and can be uncertain. The patent applications that we own may fail to result in patents with claims that cover our current and future product candidates in the United States, European countries or in other territories. Even if patents do successfully issue, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated and our patents and patent applications may not adequately protect our intellectual property, or our current and future product candidates, and may not prevent others from designing around our claims.

If the patent applications we hold and/or have out-licensed with respect to our product candidates fail to issue or if their breadth or strength of protection is threatened, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize, future products. We cannot offer any assurances about which, if any, patents will issue or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. A patent may be challenged through one or more of several administrative proceedings including Inter Partes Review, Post Grant Review, re-examination or opposition before the U.S. Patent and Trademark Office, or the USPTO, or European Patent Office, or the EPO, and by way of similar proceedings in certain other jurisdictions. For example, re-examination of, or oppositions to, patents owned by us have previously been initiated, and while we believe these concluded proceedings did not result in a commercially relevant impact on the individual patents, any successful challenge of patents or any other patents owned by us could deprive us of rights necessary for the successful commercialization of any product candidates that we or our strategic alliance partners may develop. Since patent applications in the United States and most other countries are confidential for a period of up to 18 months after filing, and some remain confidential until issued, we cannot be certain that we were the first to file any patent application related to a product candidate or an siRNA related technology or method. Furthermore, in certain situations, if we and one or more third parties have filed patent applications in the United States claiming the same subject matter, an administrative proceeding, known as a derivation proceeding (previously known as an interference), can be initiated to determine which applicant is entitled to the patent on that subject matter. Such administrative proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications, or those of our alliance partners. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to us from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms or at all. Our defense of a patent or patent application in such a proceeding may not be successful and, even if successful, may result in narrowed claims, and at substantial costs and distraction to our management and other employees.

In addition, patents have a limited lifespan. In the United States and many other countries and regions of the world including Europe, the natural expiration of a patent is generally 20 years after it is filed as a non-provisional patent application, or a PCT international patent application. Various extensions may be available, however, the life of a patent and the protection it affords is limited. Once the patent life has expired for a product, we may be open to competition from generic medications. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced.

In addition to the protection afforded by patents, we 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. Although each of our Silence Therapeutics GmbH employees either has to assign their inventions to us under German Employee Invention Law, or agrees to assign their inventions to us through an employee inventions agreement, and all of our employees, consultants, advisers and any third parties who have access to our proprietary know-how, information or technology enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or 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 confidential proprietary information, or independently develop substantially equivalent information and techniques. In addition, others may independently discover our trade secrets, proprietary know-how and

information. For example, the FDA, as part of its transparency initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property in the United States, Europe and in other jurisdictions. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Third-party claims of intellectual property infringement may prevent or delay our development and commercialization efforts.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and life sciences industries, including patent infringement lawsuits. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we and our strategic collaborators are pursuing development candidates and technologies.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to sequences, structures, materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates that are broad enough to cover one of our product candidates or use of our technologies. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in patents with claims that our product candidates or use of our technologies may infringe. In addition, third parties may have or may obtain in the future patents and assert that our product candidates or use of our technologies infringes upon one or more claims of these patents. If any third-party patents were held by a court of competent jurisdiction to be valid and enforceable and to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire. Similarly, if any third-party patents were held by a court of competent jurisdiction to be valid and enforceable and to cover aspects of our compositions, formulations, processes for manufacture or methods of use, including combination therapy, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of our management, other employees and resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including up to treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe our patents or the patents of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming, even if we ultimately prevail. For example, in 2017, we commenced patent infringement litigation against Alnylam Pharmaceuticals Inc., or Alnylam. In December 2018, we and Alnylam entered into a settlement and license agreement to settle the litigation, which was related to Alnylam's RNAi product ONPATPRO. As part of the settlement, we now

license specified patents to Alnylam, and Alnylam pays us a tiered royalty of up to one percent of its net sales of ONPATR0 in the European Union.

In addition to the costs and potential distraction associated with enforcing our patents in a lawsuit, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Our efforts in a litigation may fail and, even if successful, may result in substantial costs and be a distraction to our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

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. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our ADSs.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or life sciences companies. We may be subject to claims that our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

Risks Related to Our ADSs and Shares

An active trading market for our ADSs may not develop and you may not be able to resell your ADSs at or above the price you pay for them, if at all.

Our ADSs have been listed on Nasdaq since September 8, 2020. There can be no assurance that an active trading market for the ADSs will be sustained. The lack of an active trading market may also reduce the fair market value of the ADSs.

The trading price of our ADSs may be volatile, and you could lose all or part of your investment.

The trading price of our ADSs is likely to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their ADSs at or above the price paid for the ADSs. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, factors that are expected to affect the market price of our securities include:

- the commencement, enrollment or results of our planned and future clinical trials;
- positive or negative results from, or delays in, testing and clinical trials by us, collaborators or competitors;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates and technologies;

- the loss of any of our key scientific or management personnel;
- regulatory, legal or tax developments in the United States, United Kingdom, the European Union and other countries;
- the success of competitive products or technologies;
- adverse actions taken by regulatory agencies with respect to our clinical trials or manufacturers;
- changes or developments in laws or regulations applicable to our product candidates or technologies;
- changes to our relationships with collaborators, manufacturers or suppliers;
- concerns regarding the safety of our product candidates;
- announcements concerning our competitors or the pharmaceutical industry in general;
- actual or anticipated fluctuations in our operating results;
- changes in financial estimates or recommendations by securities analysts;
- potential acquisitions, financings, collaborations or other corporate transactions;
- the trading volume of our ADSs on Nasdaq;
- coordinated trading in our ordinary shares and/or ADSs by third parties, including market manipulation;
- publication of information in the media, including online blogs and social media, about our company by third parties;
- sales of our ADSs or ordinary shares by us, members of our senior management and directors or our shareholders;
- general economic, political, and market conditions and overall fluctuations in the financial markets in the United States, the United Kingdom, the European Union, and other countries, including impact of the Ukraine-Russia War and further global and regional impacts of the COVID-19 pandemic;
- stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biopharmaceutical industry; and
- investors' general perception of us and our business.

These and other market and industry factors may cause the market price and demand for our ADSs to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from selling their ADSs at or above the price paid for the ADSs and may otherwise negatively affect the liquidity of our ADSs.

Some companies that have experienced volatility in the trading price of their shares have been the subject of securities class action litigation. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms.

Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our business practices. Defending against litigation is costly and time-consuming and could divert our management's and key employees' attention and our resources. Furthermore, during the course of litigation,

there could be negative public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a negative effect on the market price of our ADSs.

Future sales, or the possibility of future sales, of a substantial number of our ADSs or our ordinary shares could adversely affect the price of such securities.

Future sales of a substantial number of ADSs or ordinary shares, or the perception that such sales will occur, could cause a decline in the market price of our ADSs. If holders sell substantial amounts of ADSs on Nasdaq, or if the market perceives that such sales may occur, the market price of the ADSs and our ability to raise capital through an issue of equity securities in the future could be adversely affected.

If equity research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business or our market, the price and trading volume of our ADSs could decline.

The trading market for our ADSs will be influenced by the research and reports that equity research analysts publish about us and our business. As a company admitted to trading on Nasdaq, our equity securities are currently subject to coverage by a number of analysts. However, we do not currently have and may never obtain broad research coverage by equity research analysts published in the United States. Equity research analysts may elect not to provide research coverage of our ADSs, and such lack of research coverage may adversely affect the market price of our ADSs. We will not have any control over the analysts or the content and opinions included in their reports. The price of our ADSs could decline if one or more equity research analysts downgrade our ADSs or issue other unfavorable commentary or research about us. If one or more equity research analysts ceases coverage of us or fails to publish reports on us regularly, demand for our ADSs could decrease, which in turn could cause the trading price or trading volume of our ADSs to decline.

Concentration of ownership of our ordinary shares (including ordinary shares represented by ADSs) among our existing senior management, directors and principal shareholders may prevent new investors from influencing significant corporate decisions and matters submitted to shareholders for approval.

Members of our senior management, directors and current beneficial owners of 5% or more of our ordinary shares and their respective affiliates, in the aggregate, beneficially owned approximately 71% of our issued and outstanding ordinary shares, based on the number of ordinary shares issued and outstanding as of March 1, 2023. As a result, depending on the level of attendance at general meetings of our shareholders, these persons, acting together, would be able to significantly influence all matters requiring shareholder approval, including the election, re-election and removal of directors, any merger, scheme of arrangement, or sale of all or substantially all of our assets, or other significant corporate transactions, and amendments to our articles of association. In addition, these persons, acting together, may have the ability to control the management and affairs of our company. Accordingly, this concentration of ownership may harm the market price of our ADSs by:

- delaying, deferring, or preventing a change in control;
- entrenching our management and/or the board of directors;
- impeding a merger, scheme of arrangement, takeover, or other business combination involving us; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us.

In addition, some of these persons or entities may have interests different than yours. For example, because many of these shareholders purchased their shares at prices substantially below the current market price of our ordinary shares and have held their shares for a longer period, they may be more interested in selling our company to an acquirer than other investors, or they may want us to pursue strategies that deviate from the interests of other shareholders.

Because we do not anticipate paying any cash dividends on our ordinary shares (including ordinary shares represented by ADSs) in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment.

You should not rely on an investment in our ADSs to provide dividend income. Under current English law, a company's accumulated realized profits must exceed its accumulated realized losses (on a non-consolidated basis) before dividends can be paid. Therefore, we must have distributable profits before issuing a dividend. We have never declared or paid a dividend on our ordinary shares in the past, and we currently intend to retain our future earnings, if any, to fund the development of our technologies and product candidates and the growth of our business. As a result, capital appreciation, if any, on our ADSs will be your sole source of gains for the foreseeable future. Investors seeking cash dividends should not purchase our ADSs.

We incur increased costs as a result of having our ADSs listed in the United States, and our senior management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a company whose securities are publicly listed in the United States, and particularly after we no longer qualify as an "emerging growth company," or EGC, we incur significant legal, accounting and other expenses that we did not incur prior to the listing of the ADSs on Nasdaq in the third quarter of 2020. For example, the Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and the Consumer Protection Act, the listing requirements of Nasdaq and other applicable U.S. securities rules and regulations impose various requirements on non-U.S. reporting public companies, including the establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our senior management and other personnel need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and have made some activities more time-consuming and costly. For example, it has become more difficult and more expensive for us to obtain director and officer liability insurance.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, regardless of whether or not we are an EGC we will be required to furnish a report by our senior management on our internal control over financial reporting. However, while we remain an EGC we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To prepare for eventual compliance with Section 404, including the attestation report required once we no longer qualify as an EGC, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants, adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented, and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404.

As a result of the enhanced disclosure requirements of the U.S. securities laws, business and financial information that we report is broadly disseminated and highly visible to investors, which we believe may increase the likelihood of threatened or actual litigation, including by competitors and other third parties, which could, even if unsuccessful, divert financial resources and the attention of our management and key employees from our operations.

We have previously identified material weaknesses in our internal control over financial reporting that have since been remediated. If we experience additional material weaknesses or deficiencies in the future or otherwise fail to maintain an effective system of internal controls, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect our business.

In connection with the preparation of our financial statements for the year ended December 31, 2020, we identified material weaknesses in our internal controls over our financial close and reporting process. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting such that there is a reasonable possibility that a material misstatement of annual or interim financial statements will not be prevented or detected and corrected on a timely basis. As previously disclosed in our Annual Report on Form 20-F for the year ended December 31, 2020, the material weaknesses identified related to controls to address timely reconciliation and analysis of certain key accounts, including those related to revenue recognition and the recognition and accrual of research and

development related expenses such as CRO and CMO activities. The material weaknesses arose because of insufficient business processes, related internal controls, and financial resources at the time to satisfy the additional accounting and financial reporting requirements required for a publicly U.S. listed company.

While we developed a detailed plan to address the material weaknesses and were successful in remediating them in the year ended December 31, 2021, there can be no assurance that we will not identify additional control deficiencies or material weaknesses in the future.

In addition, if we identify new material weaknesses in the future, if we are unable to comply with the requirements of Section 404, in a timely manner, if we are unable to assert that our internal control over financial reporting is effective or if our independent registered public accounting firm is unable to express an opinion as to the effectiveness of our internal control over financial reporting, the accuracy and timing of our financial reporting may be adversely affected, potentially resulting in restatements of our financial statements, we may be unable to maintain compliance with securities law requirements regarding timely filing of periodic reports and applicable Nasdaq listing requirements, investors may lose confidence in our financial reporting, and our share price may decline as a result.

We are an “emerging growth company,” and the reduced disclosure requirements applicable to emerging growth companies may make our ADSs less attractive to investors.

We are an EGC as defined in the SEC’s rules and regulations and we will remain an EGC until the earlier to occur of (1) the last day of 2025, (2) the last day of the fiscal year in which we have total annual gross revenues of at least \$1.235 billion, (3) the last day of the fiscal year in which we are deemed to be a “large accelerated filer” under SEC rules, which means the market value of our equity securities that is held by non-affiliates exceeds \$700 million as of the prior June 30th, and (4) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period. For so long as we remain an EGC, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not EGCs. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404;
- not being required to comply with any requirement that has or may be adopted by the PCAOB regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- an exemption from the requirement to seek nonbinding shareholder advisory votes on executive compensation or golden parachute arrangements.

We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of reduced reporting burdens in this report. In particular, we have not included all of the executive compensation information that would be required if we were not an EGC. We cannot predict whether investors will find our ADSs less attractive if we rely on certain or all of these exemptions. If some investors find our ADSs less attractive as a result, there may be a less active trading market for our ADSs and our ADS price may be more volatile.

We qualify as a foreign private issuer and, as a result, we will not be subject to U.S. proxy rules and will be subject to Exchange Act reporting obligations that, to some extent, are more lenient and less frequent than those of a U.S. domestic public company.

We report under the Exchange Act as a non-U.S. company with foreign private issuer status. Because we qualify as a foreign private issuer under the Exchange Act, we are exempt from certain provisions of the Exchange Act that are applicable to U.S. domestic public companies, including (i) the sections of the Exchange Act regulating the solicitation of proxies, consents or authorizations in respect of a security registered under the Exchange Act; (ii) 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 (iii) the rules under the Exchange

Act requiring the filing with the SEC of quarterly reports on Form 10-Q containing unaudited financial and other specified information, or current reports on Form 8-K upon the occurrence of specified significant events. In addition, foreign private issuers are not required to file their annual report on Form 20-F until 120 days after the end of each fiscal year, while U.S. domestic issuers that are accelerated filers are required to file their annual report on Form 10-K within 75 days after the end of each fiscal year. Foreign private issuers also are exempt from Regulation Fair Disclosure, aimed at preventing issuers from making selective disclosures of material information. As a result of the above, you may not have the same protections afforded to shareholders of companies that are not foreign private issuers.

As a foreign private issuer, we are permitted to adopt certain home country practices in relation to corporate governance matters that differ significantly from Nasdaq corporate governance listing standards. These practices may afford less protection to shareholders than they would enjoy if we complied fully with Nasdaq corporate governance listing standards.

As a foreign private issuer listed on Nasdaq, we are subject to corporate governance listing standards. However, Nasdaq rules permit a foreign private issuer like us to follow the corporate governance practices of its home country in lieu of certain Nasdaq corporate governance listing standards. Certain corporate governance practices in England, which is our home country, may differ significantly from Nasdaq corporate governance listing standards. For example, neither the corporate laws of England nor our articles of association require a majority of our directors to be independent; we may include non-independent directors as members of our nominations and remuneration committees; and our independent directors are not required to hold regularly scheduled meetings at which only independent directors are present. Therefore, our shareholders may be afforded less protection than they otherwise would have under Nasdaq corporate governance listing standards applicable to U.S. domestic issuers. See “Item 16.G. Corporate Governance” for the exemptions to the Nasdaq corporate governance rules applicable to foreign private issuers.

We may lose our foreign private issuer status, which would then require us to comply with the Exchange Act’s domestic reporting regime and cause us to incur significant legal, accounting and other expenses.

As a foreign private issuer, we are not required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers. We may no longer be a foreign private issuer as of June 30, 2023, which would require us to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers as of January 1, 2024. In order to maintain our current status as a foreign private issuer, either (a) a majority of our voting securities must be either directly or indirectly owned of record by non-residents of the United States or (b)(i) a majority of our executive officers or directors cannot be U.S. citizens or residents, (ii) more than 50% of our assets must be located outside the United States and (iii) our business must be administered principally outside the United States. If we lose our status as a foreign private issuer, we would be required to comply with the Exchange Act reporting and other requirements applicable to U.S. domestic issuers, which are more detailed and extensive than the requirements for foreign private issuers. We may also be required to make changes in our corporate governance practices in accordance with various SEC and Nasdaq rules. The regulatory and compliance costs to us under U.S. securities laws if we are required to comply with the reporting requirements applicable to a U.S. domestic issuer may be significantly higher than the cost we would incur as a foreign private issuer. As a result, we expect that a loss of foreign private issuer status would increase our legal and financial compliance costs and would make some activities highly time consuming and costly. We also expect that if we were required to comply with the rules and regulations applicable to U.S. domestic issuers, it would make it more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage and/or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our board of directors.

Holders of our ADSs have fewer rights than our shareholders and must act through the depository to exercise their rights.

Holders of our ADSs do not have the same rights as our shareholders who hold our ordinary shares directly and may only exercise their voting rights with respect to the underlying ordinary shares in accordance with the provisions of the deposit agreement. Holders of the ADSs will appoint the depository or its nominee as their representative to exercise the voting rights attaching to the ordinary shares represented by the ADSs. When a general meeting is

convened, if you hold ADSs, you may not receive sufficient notice of a shareholders' meeting to permit you to withdraw the ordinary shares underlying your ADSs to allow you to vote with respect to any specific matter. We will use commercially reasonable efforts to cause the depositary to extend voting rights to you in a timely manner, but we cannot assure you that you will receive voting materials in time to instruct the depositary to vote, and it is possible that you, or persons who hold their ADSs through brokers, dealers or other third parties, will not have the opportunity to exercise a right to vote. Furthermore, the depositary will not be liable for any failure to carry out any instructions to vote, for the manner in which any vote is cast or for the effect of any such vote. As a result, you may not be able to exercise your right to vote and you may lack recourse if your ADSs are not voted as you request. In addition, in your capacity as an ADS holder, you will not be able to call a shareholders' meeting.

You may be subject to limitations on transfers 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 deemed necessary or advisable by it in good faith in connection with the performance of its duties or at our reasonable written request, subject in all cases to compliance with applicable U.S. securities laws. 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, subject to certain rights to cancel ADSs and withdraw the underlying ordinary shares. Temporary delays in the cancellation of ADSs and withdrawal of the underlying ordinary shares may arise because the depositary has closed its transfer books or we have closed our transfer books, the transfer of ordinary shares is blocked to permit voting at a shareholders' meeting, or because we are paying a dividend on our ordinary shares or similar corporate actions.

In addition, holders of ADSs may not be able to cancel their ADSs and withdraw the underlying ordinary shares when they owe money for fees, taxes and similar charges and when it is necessary to prohibit withdrawals in order to comply with any laws or governmental regulations that apply to the ADSs or to the withdrawal of our ordinary shares or other deposited securities.

The depositary for our ADSs is entitled to charge holders fees for various services, including annual service fees.

The depositary for our ADSs is entitled to charge holders fees for various services, including for the issuance of ADSs upon deposit of ordinary shares, cancellation of ADSs, distributions of cash dividends or other cash distributions, distributions of ADSs pursuant to share dividends or other free share distributions, distributions of securities other than ADSs and annual service fees. In the case of ADSs issued by the depositary into The Depository Trust Company, or DTC, the fees will be charged by the DTC participant to the account of the applicable beneficial owner in accordance with the procedures and practices of the DTC participant as in effect at the time. The depositary for our ADSs will not generally be responsible for any U.K. stamp duty or stamp duty reserve tax arising upon the issuance or transfer of ADSs.

You may not receive distributions on our ordinary shares represented by the ADSs or any value for them if it is illegal or impractical to make them available to holders of ADSs.

Although we do not have any present plans to declare or pay any dividends, in the event we declare and pay any dividend, the depositary for the ADSs has agreed to pay to you the cash dividends or other distributions it or the custodian receives on our ordinary shares or other deposited securities after deducting its fees and expenses, or withholding of taxes. You will receive these distributions in proportion to the number of our ordinary shares your ADSs represent. However, in accordance with the limitations set forth in the deposit agreement, it may be unlawful or impractical to make a distribution available to holders of ADSs. We have no obligation to register under U.S. securities laws any offering of ADSs, ordinary shares or other securities received through such distributions. We also have no obligation to take any other action to permit distribution on the ADSs, ordinary shares, rights or anything else to holders of the ADSs. This means that you may not receive the distributions we make on our ordinary shares or any value from them if it is unlawful or impractical to make them available to you. These restrictions may have an adverse effect on the value of your ADSs.

Your right to participate in any future rights offerings may be limited, which may cause dilution to your holdings.

Under English law, shareholders usually have preemptive rights to subscribe on a pro rata basis in the issuance of new shares for cash. The exercise of preemptive rights by certain shareholders not resident in the United Kingdom may be restricted by applicable law or practice in the United Kingdom and overseas jurisdictions. We may from time to time distribute rights to our shareholders, including rights to acquire our securities. However, we cannot make rights available to you in the United States unless we register the rights and the securities to which the rights relate under the Securities Act or an exemption from the registration requirements is available. Also, under the deposit agreement, the depositary bank will not make rights available to you unless either both the rights and any related securities are registered under the Securities Act, or the distribution of them to ADS holders is exempted from registration under the Securities Act. We are under no obligation to file a registration statement with respect to any such rights or securities or to endeavor to cause such a registration statement to be declared effective. Moreover, we may not be able to establish an exemption from registration under the Securities Act. If the depositary does not distribute the rights, it may, under the deposit agreement, either sell them, if possible, or allow them to lapse. Accordingly, you may be unable to participate in our rights offerings and may experience dilution in your holdings. We are also permitted under English law to disapply preemptive rights (subject to the approval of our shareholders by special resolution or the inclusion in our articles of association of a power to disapply such rights) and thereby exclude certain shareholders, such as overseas shareholders, from participating in a rights offering (usually to avoid a breach of local securities laws).

If we are a passive foreign investment company, there could be adverse U.S. federal income tax consequences to U.S. Holders.

Under the Internal Revenue Code of 1986, as amended, or the Code, we will be a passive foreign investment company, or PFIC, for any taxable year in which (i) 75% or more of our gross income consists of passive income, or (ii) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income (including cash). For purposes of these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as if it held its proportionate share of the assets and received directly its proportionate share of the income of such other corporation. If we are a PFIC for any taxable year during which a U.S. Holder (as defined below under "Item 10.E. Taxation—Material U.S. Federal Income Tax Considerations for U.S. Holders") holds our ADSs, the U.S. Holder may be subject to adverse tax consequences regardless of whether we continue to qualify as a PFIC, including ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred, and additional reporting requirements.

Based on estimates of our income and assets, and certain assumptions with respect to the characterization of our assets as active or passive, we do not believe we were a PFIC for our taxable year ended December 31, 2022. However, no assurances regarding our PFIC status can be provided for any past, current or future taxable year. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis and the applicable law is subject to varying interpretation. Accordingly, our U.S. counsel expresses no opinion with respect to our PFIC status for any prior, current or future taxable year.

For further discussion of the PFIC rules and the adverse U.S. federal income tax consequences in the event we are classified as a PFIC, see the section titled "Taxation—Material U.S. Federal Income Considerations for U.S. Holders."

If a United States person is treated as owning at least 10% of our ordinary shares, such United States person may be subject to adverse U.S. federal income tax consequences.

For U.S. federal income tax purposes, if a United States person is treated as owning (directly, indirectly or constructively) 10% or more of our stock by vote or value, such U.S. holder will be treated as a "United States shareholder" with respect to each "controlled foreign corporation" in our group (if any). Because our group includes at least one U.S. subsidiary, our non-U.S. subsidiaries and any non-U.S. subsidiaries we were to form or acquire in the future will be treated as controlled foreign corporations.

A United States shareholder of a controlled foreign corporation will be required to annually report and include in its U.S. federal taxable income its pro rata share of “subpart F income,” “global intangible low-taxed income” and investments in U.S. property by the controlled foreign corporations, regardless of whether we make any distributions of such income. Special rules, however, apply to United States persons that are partnerships or other pass-through entities. Certain deductions and credits for foreign income taxes paid or accrued by the controlled foreign corporation may be allowed to a corporate United States shareholder, but will not be allowed to an individual United States shareholder. We cannot provide any assurance that we will furnish to any United States shareholder the information required to comply with the reporting and tax-paying obligations discussed applicable to a United States shareholder in respect of controlled foreign corporations. Failure to comply with such reporting obligations may subject a holder of our ordinary shares that is a United States shareholder to significant monetary penalties and may prevent the statute of limitations with respect to its U.S. federal income tax return for the year for which reporting was due from starting. Holders of our ordinary shares that are United States persons should consult their tax advisors regarding the potential application of these rules to their investment in our ordinary shares.

We may be unable to use U.K. carryforward tax losses to reduce future tax payments or benefit from favorable U.K. tax legislation.

As a U.K. resident trading entity, we are subject to U.K. corporate taxation. Due to the nature of our business, we have generated losses since inception. As of December 31, 2022, we had cumulative carryforward tax losses of £167.8 million. Subject to any relevant restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the company and a major change in the nature, conduct or scale of the trade), we expect these to be available to carry forward and offset against future operating profits.

As a company that carries out extensive research and development activities, we benefit from the U.K. research and development tax credit regime under the scheme for small and medium-sized enterprises, or SMEs. Under the SME scheme, we are currently able to surrender some of our trading losses that arise from our qualifying research and development activities for a cash rebate of up to 33.35% of such qualifying research and development expenditures. Changes to the SME scheme that have been recently enacted and expected to take effect in relation to expenditure incurred on or after April 1, 2023 will reduce the research and development cash rebate under the SME scheme to an amount up to 18.6% of qualifying research and development expenditures. Proposed changes to the SME scheme that would take effect from April 1, 2023 would introduce restrictions on relief that may be claimed for expenditure on sub-contracted research and development activity outside of the U.K. The rate reduction and the proposed restrictions on the scope of the regime may impact the quantum of research and development relief that we are able to claim in the future. Furthermore, the U.K. government is currently consulting on the potential replacement of the SME scheme with a regime that would operate similarly to the existing research and development expenditure credit scheme for large companies. If the proposals in the consultation document are enacted then this could change the present treatment of sub-contracted research and development work and introduce different thresholds and caps on expenditure and relief. If enacted, the new regime would be expected to impact expenditures incurred from April 2024 onward, and could have an impact on the quantum of research and development relief that we are eligible to claim. From April 1, 2021, for credit claims in excess of £20,000, the amount of payable credit that a qualifying loss-making SME business can receive through SME research and development relief in any one year has been capped at £20,000 plus three times the company’s and certain connected parties’ total pay-as-you-earn and National Insurance Contributions liability for that year, unless the company actively manages its intellectual property and does not outsource more than 15% of its R&D to a related party. We may not be able to continue to claim payable research and development tax credits in the future if we cease to qualify as an SME, based on size criteria concerning employee headcount, turnover and gross assets. We may also be restricted in our ability to claim payable research and development tax credits in the future if we become subject to the cap on available relief. Qualifying expenditures largely are comprised of employment costs for research staff, research materials, outsourced CRO costs and R&D consulting costs incurred as part of research projects. Specified subcontracted qualifying research expenditures are eligible for a cash rebate of up to 21.67% (12.09% from April 2023).

In the event we generate revenues in the future, we may benefit from the U.K. “patent box” regime that allows profits attributable to revenues from patents or patented products to be taxed at an effective rate of 10%. As of December 31, 2022, we are the exclusive licensee or owner of 26 patent families with each family comprising several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees,

milestone fees, product revenues and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower effective rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the U.K. research and development tax credit regime or the “patent box” regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments, our business, results of operations, and financial condition may be adversely affected. This may impact our ongoing requirement for investment and the timeframes within which additional investment is required.

Changes and uncertainties in the tax system in the countries in which we have operations, could materially adversely affect our financial condition and results of operations, and reduce net returns to our shareholders.

We conduct business in the United Kingdom, Germany and the United States and file income tax returns in multiple jurisdictions. Our consolidated effective income tax rate could be materially adversely affected by several factors, including: changing tax laws, regulations and treaties, or the interpretation thereof; tax policy initiatives and reforms under consideration (such as those related to the Organization for Economic Co-Operation and Development’s, or OECD, Base Erosion and Profit Shifting, or BEPS, Project, the European Commission’s state aid investigations and other initiatives); the practices of tax authorities in jurisdictions in which we operate; the resolution of issues arising from tax audits or examinations and any related interest or penalties. Such changes may include (but are not limited to) the taxation of operating income, investment income, dividends received or (in the specific context of withholding tax) dividends paid.

Tax authorities may disagree with our positions and conclusions regarding certain tax positions, or may apply existing rules in an unforeseen manner, resulting in unanticipated costs, taxes or non-realization of expected benefits.

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, His Majesty’s Revenue & Customs, or HMRC, the U.S. Internal Revenue Service or another tax authority could challenge our allocation of income by tax jurisdiction and the amounts paid between our affiliated companies pursuant to our intercompany arrangements and transfer pricing policies, including amounts paid with respect to our intellectual property development. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a “permanent establishment” under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions.

A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, for example where there has been a technical violation of contradictory laws and regulations that are relatively new and have not been subject to extensive review or interpretation, in which case we expect that we might contest such assessment. High-profile companies can be particularly vulnerable to aggressive application of unclear requirements. Many companies must negotiate their tax bills with tax inspectors who may demand higher taxes than applicable law appears to provide. Contesting such an assessment may be a lengthy and costly process and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable.

Protections found in provisions under the U.K. City Code on Takeovers and Mergers, or the Takeover Code, may delay or discourage a takeover attempt, including attempts that may be beneficial to holders of our ADSs.

The Takeover Code applies to an offer for a public company whose securities have been admitted to trading on a multilateral trading facility in the United Kingdom which includes AIM, at any time during the 10 years prior to the relevant date of an offer, provided that (i) the registered office of the company is in the United Kingdom and (ii) the company is considered by the Panel on Takeovers and Mergers, or the Takeover Panel, to have its place of central management and control in the United Kingdom. The way in which the test for central management and control is applied for the purposes of the Takeover Code may be different from the way in which it is applied by the U.K. tax authorities. Under the Takeover Code, the Takeover Panel looks to where the majority of the directors are resident, among other factors, for the purposes of determining where a company has its place of central management and control.

The Takeover Panel has confirmed that based on the current composition of our board, the Takeover Code will continue to apply to us. However, the Takeover Code could cease to apply in the future if any changes to the board composition result in the majority of the directors not being resident in the United Kingdom, Channel Islands and Isle of Man. Our articles of association have been amended to include certain important protections which would apply in the event that the Takeover Code ceases to apply.

The Takeover Code provides a framework within which takeovers of certain companies organized in the United Kingdom are regulated and conducted. The following is a brief summary of some of the most important rules of the Takeover Code:

- In connection with a potential offer, if, following an approach by or on behalf of a potential bidder, the company is “the subject of rumor or speculation” or there is an “untoward movement” in the company’s share price, there is a requirement for the potential bidder to make a public announcement about a potential offer for the company, or for the company to make a public announcement about its review of a potential offer.
- When a person or group of persons acting in concert (a) acquires, whether by a series of transactions over a period of time or not, interests in shares carrying 30% or more of the voting rights of a company (which percentage is treated by the Takeover Code as the level at which effective control is obtained) or (b) increases the aggregate percentage interest they have when they are already interested in not less than 30% and not more than 50%, they must make a cash offer to all other shareholders at the highest price paid by them or any person acting in concert with them in the 12 months before the offer was announced.
- When interests in shares carrying 10% or more of the voting rights of a class have been acquired for cash by an offeror (i.e. a bidder) or any person acting in concert with them in the offer period (i.e. before the shares subject to the offer have been acquired) or within the previous 12 months, the offer must be in cash or be accompanied by a cash alternative for all shareholders of that class at the highest price paid by the offeror or any person acting in concert with them in that period. Further, if an offeror or any person acting in concert with them acquires for cash any interest in shares during the offer period, the offer must be in cash or accompanied by a cash alternative at a price at least equal to the price paid for such shares during the offer period.
- If after an announcement of a firm offer is made, the offeror or any person acting in concert with them acquires an interest in shares in an offeree company (i.e. a target) at a price higher than the value of the offer, the offer must be increased accordingly.
- The board of directors of the offeree company must appoint a competent independent adviser whose advice on the financial terms of the offer must be made known to all the shareholders, together with the opinion of the board of directors of the offeree company.
- Favorable deals for selected shareholders are not permitted, except in certain circumstances where independent shareholder approval is given and the arrangements are regarded as fair and reasonable in the opinion of the financial adviser to the offeree company.
- All shareholders must be given the same information.
- Those issuing documents in connection with a takeover must include statements taking responsibility for the contents thereof.
- Profit forecasts, quantified financial benefits statements and asset valuations must be made to specified standards and must be reported on by professional advisers.
- Misleading, inaccurate or untrue statements made in documents or to the media must be publicly corrected immediately.

- Actions during the course of an offer by the offeree company which might frustrate the offer are generally prohibited unless shareholders approve these plans. Frustrating actions would include, for example, lengthening the notice period for directors under their service contract or agreeing to sell off material parts of the target group.
- Stringent requirements are laid down for the disclosure of dealings in relevant securities during an offer, including the prompt disclosure of positions and dealings in relevant securities by the parties to an offer and any person who is interested (directly or indirectly) in 1% or more of any class of relevant securities.
- Employees of both the offeror and the offeree company and the trustees of the offeree company's pension scheme must be informed about an offer. In addition, the offeree company's employee representatives and pension scheme trustees have the right to have a separate opinion on the effects of the offer on employment appended to the offeree board of directors' circular or published on a website.

The rights of our shareholders may differ from the rights typically offered to shareholders of a U.S. corporation.

We are incorporated under English law. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of our ADSs, are governed by English law, including the provisions of the U.K. Companies Act 2006, or the Companies Act, and by our articles of association. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations. See "Description of Share Capital and Articles of Association—Differences in Corporate Law" filed as Exhibit 2.3 to this report for a description of the principal differences between the provisions of the Companies Act applicable to us and, for example, the Delaware General Corporation Law relating to shareholders' rights and protections.

As an English company, certain capital structure decisions will require shareholder approval, which may limit our flexibility to manage our capital structure.

English law provides that a board of directors may only allot shares (or grant rights to subscribe for, or to convert any security into, shares) with the prior authorization of shareholders by ordinary resolution, being a resolution passed by a simple majority of votes cast, such authorization stating the aggregate nominal amount of shares that it covers and being valid for a maximum period of five years, each as specified in the articles of association or relevant shareholder resolution. In either case, this authorization would need to be renewed by our shareholders upon expiration (i.e., at least every five years). Typically, English public companies renew the authorization of their directors to allot shares on an annual basis at their annual general meeting.

English law also generally provides shareholders with preemptive rights when new shares are issued for cash. However, it is possible for the articles of association, or for shareholders to pass a special resolution at a general meeting, being a resolution passed by at least 75% of the votes cast, to disapply preemptive rights. Such a disapplication of preemptive rights may be for a maximum period of up to five years from the date of adoption of the articles of association, if the disapplication is contained in the articles of association, or from the date of the shareholder special resolution, if the disapplication is by shareholder special resolution, but not longer than the duration of the authority to allot shares to which the disapplication relates. In either case, this disapplication would need to be renewed by our shareholders upon its expiration (i.e., at least every five years). Typically, English public companies renew the disapplication of preemptive rights on an annual basis at their annual general meeting.

English law also generally prohibits a public company from repurchasing its own shares without the prior approval of shareholders by ordinary resolution, being a resolution passed by a simple majority of votes cast, and other formalities. Such approval may be for a maximum period of up to five years. See "Description of Share Capital and Articles of Association" filed as Exhibit 2.3 to this report.

Claims of U.S. civil liabilities may not be enforceable against us.

We are incorporated under English law. Substantially all of our assets are located outside the United States. The majority of our senior management and board of directors reside outside the United States. As a result, it may not be

possible for investors to effect service of process within the United States upon such persons or to enforce judgments obtained in U.S. courts against them or us, including judgments predicated upon the civil liability provisions of the U.S. federal securities laws.

The United States and the United Kingdom do not currently have a treaty providing for the reciprocal recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in England and Wales. In addition, uncertainty exists as to whether the English and Welsh courts would entertain original actions brought in England and Wales against us or our directors or senior management predicated upon the securities laws of the United States or any state in the United States. Any final and conclusive monetary judgment for a definite sum obtained against us in U.S. courts would be treated by the courts of England and Wales as a cause of action in itself and sued upon as a debt so that no retrial of the issues would be necessary, provided that certain requirements are met consistent with English law and public policy. Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the U.S. securities laws is an issue for the English court making such decision. If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose.

As a result, U.S. investors may not be able to enforce against us or our senior management, board of directors or certain experts named herein who are residents of the United Kingdom or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

Our articles of association provide that the U.S. federal district courts are the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act.

Our articles of association provide that the U.S. federal district courts are the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. However, the enforceability of similar federal court choice of forum provisions has been challenged in legal proceedings in the United States, and it is possible that a court could find this type of provision to be inapplicable, unenforceable, or inconsistent with other documents that are relevant to the filing of such lawsuits. In addition, the Securities Act provides that both federal and state courts have jurisdiction over suits brought to enforce any duty or liability under the Securities Act or the rules and regulations thereunder. Accepting or consent to this forum selection provision does not constitute a waiver by you of compliance with federal securities laws and the rules and regulations thereunder. You may not waive compliance with federal securities laws and the rules and regulations thereunder. If a court were to find the choice of forum provision contained in our articles of association to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our results of operations and financial condition. This choice of forum provision may limit a shareholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits.

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

The deposit agreement governing our ADSs provides that owners and holders of ADSs irrevocably waive the right to a trial by jury in any legal proceeding arising out of or relating to the deposit agreement or the ADSs, including claims under U.S. federal securities laws, against us or the depository to the fullest extent permitted by applicable law. If this jury trial waiver provision is prohibited by applicable law, an action could nevertheless proceed under the terms of the deposit agreement with a jury trial. Although we are not aware of a specific federal decision that addresses the enforceability of a jury trial waiver in the context of U.S. federal securities laws, it is our understanding that jury trial waivers are generally enforceable. Moreover, insofar as the deposit agreement is governed by the laws of the State of New York, New York laws similarly recognize the validity of jury trial waivers in appropriate circumstances. In determining whether to enforce a jury trial waiver provision, New York courts and federal courts will consider whether the visibility of the jury trial waiver provision within the agreement is sufficiently prominent such that a party has knowingly waived any right to trial by jury. We believe that this is the case with respect to the deposit agreement and the ADSs.