PART I

Item 1. Identity of Directors, Senior Management

Not applicable.

Item 2. Offer Statistics and Expected Timetable

Not applicable.

Item 3. Key Information

3A. Selected Financial Data

Reserved.

3B. Capitalization and Indebtedness

Not applicable.

3C. Reasons for the offer and use of proceeds

Not applicable.

3D. Risk Factors

Investing in our securities involves a high degree of risk. You should consider and read carefully all of the risks and uncertainties described below, as well as other information included in this annual report, including our consolidated financial statements and related notes included elsewhere in this annual report, before making an investment decision. If any of the following risks actually occur, it could harm our business, prospects, results of operations and financial condition. In such event, the trading price of the ADSs could decline and you might lose all or part of your investment. You should not interpret our disclosure of any of the following risks to imply that such risks have not already materialized.

Risk Factors Summary

Our business is subject to a number of risks and uncertainties, including those risks discussed at-length below this summary. These risks include, among others, the following:

Risks Related to our Financial Position and Need for Capital

- We have not received approval for any product candidate for commercial sale and, as a result, we have never generated any revenue, have incurred significant financial losses and expect to continue to incur significant financial losses in the future, which makes it difficult to assess our future viability.
- We will require additional capital in the future, which may not be available to us on commercially favorable terms, or at all. Raising additional capital may cause dilution to holders of our ADSs.

Risks Related to Development and Commercialization of Our Product Candidate

- Clinical trials being conducted to test our product candidate, OPT-302, may not obtain the desired safety and efficacy results or may be delayed or more costly than anticipated.
- We may encounter difficulties in enrolling patients in our clinical trials.
- OPT-302 may be shown to cause undesirable side effects or other adverse events that could delay or prevent its regulatory approval, limit its commercial profile or result in significant negative consequences following regulatory approval, if such approval is granted.

- The marketing approval process is expensive, time-consuming and uncertain, and even if OPT-302 receives marketing approval, we may not be successful in our commercialization efforts and OPT-302 may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.

- We may face substantial competition, which may result in others discovering, developing or commercializing competing products before or more successfully than us.

- Our business could be negatively affected by the effects of health epidemics, including the evolving effects of the COVID-19 pandemic, in regions where we or third parties on which we rely have significant manufacturing facilities, concentrations of clinical trial sites or other business operations.

Risks Related to Legal and Regulatory Compliance Matters

- Disruptions at the FDA could delay or prevent new products from being developed, approved or commercialized.

- Changes in U.S. healthcare law may impact our business in ways that we cannot currently predict.

- We are subject to economic, political, regulatory and other risks associated with international operations.

Risks Related to Our Reliance on Third Parties

- We rely on third-party manufacturers to produce OPT-302 or any future product candidates. If such manufacturers do not produce acceptable product candidates, this could have a material adverse effect on our business.

- We are currently dependent on third parties to conduct clinical trials and some aspects of our research and development activities. Such third parties may not perform satisfactorily, including failing to meet deadlines for completion of such trial, research or testing.

Risks Related to Employee Matters and Managing Our Growth

- We may not be able to attract, integrate, manage and retain qualified personnel or key employees.

- We are increasing and expect to continue increasing the size of our organization. If we are unable to effectively manage the anticipated growth, our business, results of operations, cash flows, financial condition and/or prospects will be negatively affected.

Risks Related to Intellectual Property

- If we are unable to obtain and maintain intellectual property protection for our products and technologies, or if we are unable to protect our intellectual property rights, we may not be able to compete effectively in our markets.

- We may become involved in lawsuits to protect or enforce our intellectual property, or third parties may initiate legal proceedings against us alleging that we infringe their intellectual property rights.

- Our current intellectual property portfolio may not prove to be sufficient to protect our competitive advantage. Additional competitors could enter the market, including with biosimilar products, and sales of affected products may decline materially.

Risks Related to Ownership of the ADSs

- The rights of our shareholders may be different from the rights of shareholders in companies governed by the laws of U.S. jurisdictions.

- As a foreign private issuer and as permitted by the listing requirements of Nasdaq, we will rely on certain home country corporate governance practices rather than the corporate governance requirements of Nasdaq. We may lose our foreign private issuer status in the future, which could result in significant additional costs and expenses.

- Both foreign private issuers and emerging growth companies are also exempt from certain more stringent executive compensation disclosure rules for U.S. public companies under the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010. Even if we no longer qualify as an emerging growth company, so long as we remain a foreign private issuer, we will continue to be exempt from such compensation disclosures.

Risks Related to Our Financial Position and Need for Capital

We are a clinical stage biopharmaceutical company with no products approved for commercial sale. We have incurred net losses since our inception, we expect to incur significant losses and increasing operating losses for the foreseeable future, and we may never be profitable.

We are a clinical stage biopharmaceutical company with no products approved for commercial sale. To date, our operations have been limited to organizing and staffing our company, business planning, raising capital, developing our product candidate, OPT-302, and licensing certain related technology, conducting research and development activities, including preclinical studies and clinical trials, and providing general and administrative support for these operations. Investment in biopharmaceutical product development is highly speculative because it entails substantial upfront capital expenditures and significant risk that any potential product candidate will fail to demonstrate adequate effect and/or an acceptable safety profile, gain regulatory approval and become commercially viable. We have not generated any revenue from product sales to date, and we continue to incur significant research and development and other expenses related to our ongoing operations. We are not profitable and have incurred net losses since our inception. Our total comprehensive losses were US$11.1 million and US$44.9 million for the years ended June 30, 2020 and 2021. As of June 30, 2021, we had an accumulated loss of US$124.1 million. We have spent, and expect to continue to spend, significant resources to fund research and development of, and seek regulatory approvals for, OPT-302 and any future product candidates. We expect to incur substantial and increasing operating losses over the next several years as our research, development, manufacturing and clinical trial activities increase. Additionally, if OPT-302 is approved for commercial sale, our commercialization expenses will increase significantly as we establish sales, marketing, distribution, manufacturing, supply chain and other commercial infrastructure. As a result, our accumulated losses will also increase significantly. We may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may negatively affect our business. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue. Our prior losses and expected future losses have had and will continue to have a negative impact on our total (deficit) equity and working capital. The net losses we incur may fluctuate significantly from quarter-to-quarter such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. Even if we eventually generate product revenue, we may never be profitable and, if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis.

We currently have no source of product revenue and may never become profitable.

OPT-302 has not been approved for commercial sale, and we expect it to be several years before OPT-302 is approved, if ever, and we are able to commence sales of OPT-302. To date, we have not generated any revenue from the licensing or commercialization of OPT-302 and do not expect to receive revenue from it for a number of years, if ever. We will not be able to generate product revenue unless and until OPT-302 or any future product candidate, alone or with future partners, successfully completes clinical trials, receives regulatory approval and is successfully commercialized. Although we may seek to obtain revenue from collaboration or licensing agreements with third parties, we currently have no such agreements that could provide us with material, ongoing future revenue and we may never enter into any such agreements. Our ability to generate future product revenue from OPT-302 or any future product candidates also depends on a number of additional factors, including our or our future partners' ability to:

- successfully complete research and clinical development of OPT-302 and any future product candidates and obtain regulatory approvals for commercialization;

- maintain supply and manufacturing relationships with third parties, and ensure adequate and legally compliant manufacturing of bulk drug substances and drug products to maintain that supply, including any scale up of manufacturing processes for OPT-302 to support our planned Phase 3 clinical program of OPT-302 in combination with anti-vascular endothelial growth factor-A, or anti-VEGF-A, therapy for the treatment of wet age-related macular degeneration, or AMD;

- launch and commercialize future product candidates for which we obtain marketing approval, if any, and, if launched independently, successfully establish a sales force, marketing and distribution infrastructure;

- demonstrate the necessary safety data post-approval to ensure continued regulatory approval;

- obtain coverage and adequate product reimbursement from third-party payors, including government payors;

- achieve market acceptance for our or our future partners' products, if any;

- establish, maintain, protect and enforce our intellectual property rights; and

- attract, hire and retain qualified personnel.

In addition, because of the numerous risks and uncertainties associated with biologic product development, including that OPT-302 may not advance through development, achieve the endpoints of applicable clinical trials or receive approval for use in combination with one or more approved therapies, we are unable to predict the timing or amount of increased expenses, or if or when we will achieve or maintain profitability. In addition, our expenses could increase beyond expectations if we decide, or are required by the U.S. Food and Drug Administration, or the FDA, or comparable non-U.S. regulatory authorities, including the European Medicines Agency, or the EMA, to perform studies or trials in addition to those that we currently anticipate. Even if we complete the development and regulatory processes described above, we anticipate incurring significant costs associated with launching and commercializing these products.

Even if we generate revenue from the sale of any of our product candidates that may be approved, we may not become profitable and may need to obtain additional funding to continue operations. If we fail to become profitable or do not sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce our operations.

We will require substantial additional capital to finance our operations, which may not be available to us on acceptable terms, or at all. As a result, we may not complete the development and commercialization of OPT-302 or develop new product candidates.

As a clinical-stage biopharmaceutical company, our operations have consumed significant amounts of cash since our inception. We expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we continue our Phase 3 clinical trials of OPT-302 in combination with anti-VEGF-A therapy for the treatment of wet AMD in, continue clinical development of OPT-302 in combination with aflibercept for the treatment of persistent diabetic macular edema, or DME, and other retinal diseases, and commence commercialization plans. Even if we are able to obtain regulatory approval for OPT-302 and any future product candidates that we may develop, we will require substantial additional capital to commercialize such product candidates.

Our forecast of the period of time through which our financial resources will adequately support our operations is a forward-looking statement and involves risks and uncertainties, and actual results could vary as a result of a number of factors, including the factors discussed elsewhere in this "Risk Factors" section. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Our future funding requirements, both short and long-term, will depend on many factors, including:

- the initiation, progress, timing, costs and results of clinical trials for OPT-302 and any future product candidates we may develop, including whether the FDA or comparable non-U.S. regulatory authorities require additional clinical trials beyond our Phase 3 clinical trials of OPT-302 in combination with anti-

VEGF-A therapy for the treatment of wet AMD to support an approved label of OPT-302 in combination with multiple existing anti-VEGF-A therapies;

- the initiation, progress, timing, costs and results of additional clinical trials and studies to evaluate the potential for co-formulation of OPT-302 with approved and/or biosimilar forms of VEGF-A inhibitors to provide flexibility of treatment options for physicians and to reduce the frequency and number of injections for patients;
- the outcome, timing and cost of seeking and obtaining regulatory approvals from the FDA and comparable non-U.S. regulatory authorities;
- if approved, the costs of commercialization activities for OPT-302, or any other product candidate that receives regulatory approval;
- the cost to establish, maintain, expand, enforce and defend the scope of our intellectual property portfolio, including the amount and timing of any payments we may be required to make, or that we may receive, in connection with licensing, preparing, filing, prosecuting, defending and enforcing of any patents or other intellectual property rights;
- our headcount growth and associated costs as we expand our research and development capabilities and establish a commercial infrastructure;
- market acceptance of any approved product candidates, including product pricing and adequate reimbursement by third-party payors;
- the cost of acquiring, licensing or investing in additional businesses, products, product candidates and technologies;
- the cost of establishing sales, marketing and distribution capabilities for OPT-302 and any future product candidates for which we may receive regulatory approval and that we determine to commercialize ourselves or in collaboration with our future partners; and
- the costs of operating as a public company with securities listed in both Australia and the United States.

We will require additional capital to develop, obtain regulatory approval for and commercialize OPT-302 and any future product candidates, including to complete our ongoing Phase 3 clinical trials for OPT-302 for the treatment of wet AMD. In particular, we will require additional capital to progress our ongoing and future planned clinical trials without delays, including payments in connection with the achievement of certain regulatory milestones. We do not have any committed external source of funds. We expect to finance future cash needs through public or private equity or debt offerings or collaborations. We also intend to continue to apply for tax incentives under the Research and Development Tax Incentive scheme provided by the Australian government. See "—Risks Related to Development and Commercialization of Our Product Candidates—We have received tax credits under the Research and Development Tax Incentive scheme in Australia that may become repayable if we did not or do not comply with the rules of the scheme, or we may become ineligible for tax credits in our current or future tax years, which could harm our business, financial condition and results of operations." Additional capital may not be available in sufficient amounts or on reasonable terms, if at all. If we are not able to raise additional capital, we may not be able to expand our operations or otherwise capitalize on our business opportunities, and our business and financial condition will be negatively impacted.

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

Holders of our ADSs could suffer dilution or be negatively affected by fixed payment obligations we may incur if we raise additional funds through the issuance of additional equity securities or debt. Further, these securities may have rights senior to those of our ordinary shares and could contain covenants or protective rights that would restrict our operations and potentially impair our competitiveness, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could negatively impact our ability to conduct our business. If we need to secure additional financing, such additional fundraising efforts may divert our management and research efforts from our

day-to-day activities, which may negatively affect our ability to develop and commercialize OPT-302 and any future product candidates.

To the extent we obtain additional funding through product collaborations, these arrangements would generally require us to relinquish rights to some of our technologies, product candidates or products, and we may not be able to enter into such agreements, on acceptable terms, if at all. If we are unable to obtain additional funding on a timely basis, we may be required to curtail or terminate some or all of our development programs or product candidates.

Unstable market and economic conditions may have serious adverse consequences on our business and financial condition.

Global credit and financial markets have experienced extreme disruptions at various points over the last few decades, characterized by diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. If another such disruption in credit and financial markets and deterioration of confidence in economic conditions occurs, our business may be harmed. If the equity and credit markets were to deteriorate significantly in the future, it may make any necessary debt or equity financing more difficult to complete, more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could harm our growth strategy, financial performance and share price and could require us to delay or abandon development or commercialization plans. In addition, there is a risk that one or more of our service providers, manufacturers or other partners would not survive or be able to meet their commitments to us under such circumstances, which could directly affect our ability to attain our operating goals on schedule and on budget.

Risks Related to Development and Commercialization of Our Product Candidates

Our business substantially depends on the success of OPT-302, our only product candidate under clinical development, which has not completed a pivotal Phase 3 clinical trial. If we are unable to obtain regulatory approval for and successfully commercialize OPT-302 or any future product candidates, or we experience significant delays in doing so, our business will be harmed.

To date, the primary focus of our product development has been OPT-302 in combination with anti-VEGF-A therapy for the treatment of patients with wet AMD and DME. Currently, OPT-302 is our only product candidate under clinical development. This may make an investment in our company riskier than similar companies that have multiple product candidates in active development and that therefore may be able to better sustain a failure of a lead candidate. Successful continued development and ultimate regulatory approval of OPT-302 combination therapy for the treatment of wet AMD, DME or other indications is critical to the future success of our business. We have invested, and will continue to invest, a significant portion of our time and financial resources in the clinical development of OPT-302. If we cannot successfully develop, obtain regulatory approval for and commercialize OPT-302, we may not be able to continue our operations. The future regulatory and commercial success of OPT-302 is subject to a number of risks, including the following:

- we may not have sufficient financial and other resources to complete the necessary clinical trials for OPT-302, including, but not limited to, the pivotal clinical trials needed to obtain drug approval;
- we may not be able to obtain adequate evidence from clinical trials of efficacy and safety for OPT-302 combination therapy for the treatment of wet AMD, DME or other indications;
- in our clinical trials for OPT-302, we may need to adjust our clinical trial procedures and may need additional clinical trial sites, which could delay our clinical trial progress;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or comparable non-U.S. regulatory authorities for marketing approval;
- the standards implemented by clinical or regulatory agencies may change at any time and we cannot be certain what regulatory agencies may require in pivotal clinical trials for the approval of OPT-302;
- the results of later stage clinical trials may not be as favorable as the results we have observed to date in our preclinical studies and early clinical trials;

- we cannot be certain of the number and type of clinical trials and non-clinical studies that the FDA or comparable non-U.S. regulatory agencies will require in order to approve OPT-302 combination therapy
- for the treatment of wet AMD, DME or any other indication, including an approved label for use of OPT-302 in combination with multiple anti-VEGF-A therapies for the treatment of wet AMD;
- establishing sales, marketing and distribution capabilities and launching commercial sales of our products, if and when approved, whether alone or in collaboration with others;
- acceptance of our products, if and when approved, by patients, the medical community and third-party payors;
- obtaining and maintaining third-party coverage and adequate reimbursement;
- maintaining a continued acceptable safety profile of our products following approval, including when used in combination with existing therapies;
- effectively competing with other therapies; and
- enforcing and defending intellectual property rights and claims.

Many of these risks are beyond our control, including the risks related to clinical development, the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing and sales efforts of any future collaborator. Of the large number of drugs in development in the pharmaceutical industry, only a small percentage result in the submission of a new drug application or a biologics license application, or BLA, to the FDA and even fewer are approved for commercialization. Furthermore, even if we do receive regulatory approval to market OPT-302, any such approval may be subject to limitations on the indicated uses or patient populations for which we may market the products. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development programs, we may be unable to successfully develop or commercialize OPT-302. If we or any of our future development collaborators are unable to develop, or obtain regulatory approval for, or, if approved, successfully commercialize OPT-302, we may not be able to generate sufficient revenue to continue our business.

Clinical drug development involves a lengthy and expensive process with uncertain timelines and uncertain outcomes. Our clinical trials may fail to adequately demonstrate the safety and efficacy of OPT-302 or any future product candidates.

OPT-302 and any future product candidates will be subject to rigorous and extensive clinical trials and extensive regulatory approval processes implemented by the FDA and comparable non-U.S. regulatory authorities before obtaining marketing approval from these regulatory authorities. The drug development and approval process is lengthy and expensive, and approval is never certain. For example, we do not expect to report topline data from our Phase 3 clinical trials of OPT-302 for the treatment of wet AMD until 2023, despite FDA Fast Track designation. Investigational new drugs, such as OPT-302, may not prove to be safe and effective in clinical trials. We may be unable to conduct clinical trials at preferred sites, enlist clinical investigators, enroll sufficient numbers of participants or begin or successfully complete clinical trials in a timely fashion, if at all. In addition, the design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced.

If we experience delays in clinical testing, our commercial prospects will be harmed, our costs may increase and our business may be harmed.

Conducting clinical studies for any product candidates in the United States requires filing an investigational new drug application, or IND, and reaching agreement with the FDA on clinical protocols, finding appropriate clinical sites and clinical investigators, securing approvals for such studies from the institutional review board at each such site, manufacturing clinical quantities of product candidates and supplying drug product to clinical sites. Currently, we have an active IND with the FDA in the United States for OPT-302. If any such future IND is not approved by the FDA, our clinical development timeline may be negatively impacted and any future clinical programs may be delayed or terminated.

We cannot guarantee that we will be able to successfully accomplish required regulatory activities or all of the other activities necessary to initiate and complete clinical trials. As a result, our clinical trials may be extended, delayed or terminated, and we may be unable to obtain regulatory approvals or successfully commercialize our products. We do not know whether any other clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Our product development costs will increase if we experience delays in clinical testing. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize OPT-302 and any future product candidates or allow our competitors to bring products to market before we do, which would impair our ability to successfully commercialize OPT-302 or any future product candidates and may harm our business, results of operations and prospects. Events that may result in a delay or unsuccessful completion of clinical development include:

- the unavailability of financial resources to commence and complete planned trials;
- delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- revisions to labeling, including adding limitations on approved uses or the additions of additional warnings, contraindications or other safety information including boxed warnings;
- ongoing discussions with the FDA or comparable non-U.S. regulatory authorities regarding the scope or design of our clinical trials;
- deviations from the trial protocol by clinical trial sites and investigators, or failures to conduct the trial in accordance with regulatory requirements;
- the need to repeat clinical trials as a result of inconclusive or negative results or poorly executed testing or changes in required endpoints by the FDA or comparable non-U.S. authorities;
- unfavorable FDA inspection and review of a clinical trial site or records of any clinical or preclinical investigation;
- the placement of a clinical hold on a clinical trial by the FDA or comparable non-U.S. authorities;
- delays in obtaining, or the inability to obtain, required approvals from institutional review boards or other governing entities at clinical sites selected for participation in our clinical trials;
- failure of third parties, such as CROs, to satisfy their contractual duties to us or meet expected deadlines;
- delays in the testing, validation, manufacturing and delivery of the product candidates to the clinical sites;
- insufficient supply or deficient quality of product candidate materials or other materials necessary to conduct our clinical trials, including of drugs to be used in the proposed combination therapy with our product candidates;
- delays in enrolling participants into our clinical trials;
- delays in patients completing a trial or returning for post-treatment follow-up;
- delays caused by patients dropping out of a trial due to side effects, disease progression or otherwise;
- serious and unexpected drug-related adverse effects experienced by participants in our clinical trials;
- implementation of new, or changes to, guidance or interpretations from the FDA or comparable non-U.S. authorities with respect to approval pathways for any product candidates we are pursuing; and
- changes in government regulations or administrative actions or lack of adequate funding to continue the clinical trials.

Our or our future collaborators' inability to timely complete clinical trials could result in additional costs to us as well as impair our ability to generate product revenue, continue development, commercialize OPT-302 and any future product candidates and receive royalties on product sales. In addition, if we make changes to a product candidate, we may need to conduct additional nonclinical studies or clinical trials to bridge or demonstrate the comparability of our modified product candidate to earlier versions, which could delay our clinical development plan or marketing approval for our current product candidate and any future product candidates.

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

The timely completion of clinical trials largely depends on patient enrollment. We may encounter delays in enrolling, or be unable to enroll, a sufficient number of patients to complete any of our clinical trials, and even once enrolled, we may be unable to retain a sufficient number of patients to complete any of our trials. Many factors affect patient enrollment, including:

- the size and nature of the patient population, which may be limited due to eligibility requirements;
- the number and location of clinical sites;
- competition with other companies for clinical sites or patients;
- the availability and amount of any patient stipend;
- the eligibility and exclusion criteria for the trial;
- the design of the clinical trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- inability to obtain and maintain patient consents;
- significant adverse events or other side effects observed, if any;
- risk that enrolled participants will drop out before completion; and
- competing clinical trials and clinicians' and patients' perceptions as to the potential advantages of the drug being studied in relation to other available therapies.

In addition, other companies are conducting clinical trials for the same indications and seek to enroll patients in their trials that may otherwise be eligible for our clinical studies or trials, which could lead to slow recruitment and delays in our clinical programs. Further, since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which could further reduce the number of patients who are available for our clinical trials in these sites.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. If we are unable to enroll a sufficient number of patients that will complete clinical testing, we will be unable to seek or gain marketing approval for OPT-302 and any future product candidates and our business will be harmed. Even if we are able to enroll a sufficient number of patients in our clinical studies or trials, delays in patient enrollment may result in increased costs or may affect the timing or outcome of our clinical trials, which could prevent completion of these trials and negatively affect our ability to advance the development of OPT-302 and any future product candidates.

OPT-302 and any future product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval or limit the commercial profile of an approved label.

Undesirable side effects caused by OPT-302 combination therapy or any future product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable non-U.S. regulatory authorities. Additional clinical studies may be required to evaluate the safety profile of OPT-302 combination therapy or any

future product candidates. We have no clinical safety data on patient exposure to OPT-302 administered in combination with an anti-VEGF-A therapy for longer than 24 weeks.

Future results of our trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics, including, for example, immunogenicity. In such an event, we could suspend or terminate our trials or the FDA or comparable non-U.S. regulatory authorities could order us to cease clinical trials or deny approval of OPT-302 in combination with anti-VEGF-A therapy or any future product candidates for any or all targeted indications. Drug-related side effects could affect patient recruitment or the ability of enrolled subjects to complete the trial or result in potential product liability claims. Any of these occurrences could materially and negatively affect our business, financial condition, results of operations and prospects. While OPT-302 has been well tolerated in our completed clinical trials, dosed patients have experienced certain adverse events, including potentially treatment-related serious adverse events, or SAEs, of myocardial infarction, endophthalmitis and vitritis in our Phase 2b clinical trial of OPT-302 combination therapy for the treatment of wet AMD, and a potentially treatment-related SAE of stroke for one patient in our Phase 1b/2a clinical trial of OPT-302 combination therapy for the treatment of DME.

It may be difficult to discern whether certain events or symptoms observed during our clinical trials or by patients using our approved products are related to OPT-302 or any future product candidates or approved products, including anti-VEGF-A therapies used in combination with OPT-302, or some other factor. As a result, we and our development programs may be negatively affected even if such events or symptoms are ultimately determined to be unlikely related to OPT-302 or any future product candidates or approved products. We are developing OPT-302 to complement existing VEGF-A inhibitors, including ranibizumab and aflibercept. There are some potential side effects associated with intravitreal anti-VEGF-A therapies such as intraocular hemorrhage, intraocular pressure elevation, retinal detachment, inflammation, vasculitis, artery occlusion or infection inside the eye and over-inhibition of VEGF, as well as the potential for potential systemic side effects such as heart attack, stroke, wound healing problems and high blood pressure. Further, OPT-302 in combination with anti-VEGF-A therapies for the treatment of wet AMD is administered as sequential intravitreal injections over several weeks. There are risks inherent in the intravitreal injection procedure of drugs such as existing anti-VEGF-A therapies in combination with OPT-302 which can cause injury to the eye and other complications including conjunctival hemorrhage, punctate keratitis, eye pain, conjunctival hyperemia, which results in a discharge, intra-ocular inflammation and inflammation of the interior of the eye. For example, in our completed clinical trials, patients dosed with OPT-302 have experienced potentially treatment-related ocular adverse events such as eye pain, vitreous floaters, eye irritation and raised intraocular pressure.

We cannot assure you that additional or more severe adverse side effects than those observed to date related to OPT-302 combination therapy or any future product candidates will not be observed in our clinical trials or in the commercial setting. If observed, such adverse side effects could delay or preclude regulatory approval of OPT-302 combination therapy or any future product candidates, limit commercial use or result in the withdrawal of previously granted marketing approvals. If we or others identify undesirable or unacceptable side effects caused by OPT-302 combination therapy or any future product candidates or products:

- we may be required to modify, suspend or terminate our clinical trials;
- we may be required to modify or include additional dosage and administration instructions, warnings and precautions, contraindications, boxed warnings, limitations, restrictions or other statements in the product label for our approved products, or issue field alerts to physicians and pharmacies;
- we, or any future collaborators, may be required to create a risk evaluation and mitigation strategy, or REMS, which could include a medication guide outlining the risks of such side effects for distribution to patients, a communication plan for healthcare providers, and/or other elements to assure safe use;
- we may be required to conduct costly additional clinical trials;
- we may be subject to limitations on how we may promote our approved products;
- sales of our approved products may decrease significantly;
- regulatory authorities may require us to take our approved products off the market;

- we may be subject to regulatory investigations, government enforcement actions, litigation or product liability claims; and
- our products may become less competitive or our reputation may suffer.

Any of these results could decrease or prevent any sales of our approved product or substantially increase the costs and expenses of commercializing and marketing our product.

Even if we complete the necessary Phase 3 pivotal clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us or any future collaboration partners from obtaining approvals for the commercialization of OPT-302 for the treatment of wet AMD or any other indication as well as for any other product candidate we develop.

Any product candidate we may develop and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory authorities in the United States and by comparable non-U.S. regulatory authorities. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate in a given jurisdiction. We have not received approval to market any product candidates from regulatory authorities in any jurisdiction and it is possible that none of the product candidates we may seek to develop in the future will ever obtain regulatory approval. While we expect to expand our internal regulatory function to support the marketing approval process for OPT-302, we have no prior experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely in part on third-party CROs or regulatory consultants to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the biologic product candidate's safety, purity, efficacy and potency. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Any product candidates we develop may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and in other jurisdictions, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit, or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of any product candidates we may develop, the commercial prospects for those product candidates, including for OPT-302 in other indications, may be harmed, and our ability to generate revenues will be materially impaired.

Lack of efficacy, adverse events or undesirable side effects may emerge in clinical trials conducted by third parties with product candidates for wet AMD or DME, which could negatively affect our stock price, our ability to attract additional capital and our development program.

Lack of efficacy, adverse events or undesirable side effects may emerge in clinical trials conducted by third parties developing product candidates for wet AMD or DME. In addition, other companies have developed products for wet AMD and DME, including product candidates administered in combination with anti-VEGF-A therapies, and have suffered setbacks and clinical trial failures in the past, including failures of primary endpoints in Phase 3 pivotal clinical trials following positive data from Phase 1 and 2 trials. Lack of efficacy, adverse events or undesirable side effects experienced by subjects in third party clinical trials currently being conducted or previously conducted could negatively affect our stock price, our ability to attract additional capital and our development of OPT-302 or even the viability of OPT-302 as a product candidate. In addition, any such adverse events or undesirable side effects may lead to increased regulatory requirements for, or additional regulatory

review of, OPT-302, which may result in delays in development and commercialization of OPT-302 and harm our business, financial condition and results of operations.

The results of completed clinical trials may not be predictive of future results. Data from our clinical trials to date may not be indicative of results obtained when these trials are completed or in later stage trials.

There is a high failure rate for drugs and biologic products proceeding through clinical trials. Failure can occur at any time during the clinical trial process. The results of completed clinical trials of OPT-302 or any future product candidate may not be predictive of the results of later-stage clinical trials, including our Phase 3 trials of OPT-302 in combination with anti-VEGF-A therapy for the treatment of wet AMD, and the results of trials in certain patients may not be predictive of those obtained in another. In fact, many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late stage clinical trials even after achieving promising results in earlier stage clinical trials. In addition, data obtained from clinical activities is subject to varying interpretations, which may delay, limit or prevent regulatory approval.

The results of our Phase 2b clinical trial of OPT-302 combination therapy may not be predictive of the results of our Phase 3 clinical program due, in part, to the fact that we have no clinical data on OPT-302 in combination with anti-VEGF-A therapy in any clinical trial longer than 24 weeks and that we have begun and plan to continue to conduct our Phase 3 clinical trials at many clinical centers that were not included in our Phase 2b clinical trial. The number of patients exposed to product candidates and the average exposure time in prior clinical trials may be inadequate to detect rare adverse events or findings that may only be detected once a product candidate is administered to more patients and for greater periods of time. Any approved label for OPT-302 combination therapy may also be limited if our Phase 3 clinical trial results do not show long-term clinically significant efficacy results, including for over 12 months or in combination with either of the approved anti-VEGF-A therapies. In addition, if a combination of OPT-302 with an anti-VEGF-A therapy in our Phase 3 clinical program for the treatment of wet AMD does not achieve clinically significant superiority over anti-VEGF-A monotherapy with statistical significance on the primary endpoints of our Phase 3 clinical trials, or the FDA or a comparable non-U.S. regulatory authority requires additional clinical trials beyond our Phase 3 clinical program to support an approved label of OPT-302 used in combination with multiple anti-VEGF-A therapies, our ability to successfully commercialize OPT-302 in combination with anti-VEGF-A therapy for the treatment of wet AMD would be harmed.

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

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

In addition, adverse changes between interim data and final data could significantly harm our business and prospects. Additional disclosure of interim data by us or by our competitors in the future could also result in volatility in the price of the ADSs and our ordinary shares. Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise

regarding a particular product candidate or our business. If the topline data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, OPT-302 or any future product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

We may face substantial competition, which may result in others discovering, developing or commercializing competing products before or more successfully than us.

The biopharmaceutical industry is intensely competitive and subject to rapid innovation and significant technological advancements. We believe the key competitive factors that will affect the development and commercial success of OPT-302 and any future product candidates are efficacy, safety and tolerability profile, reliability, convenience of dosing, price, the level of generic competition and reimbursement. Our competitors include multinational pharmaceutical companies, specialized biotechnology companies, universities and other research institutions. A number of biotechnology and pharmaceutical companies are pursuing the development or marketing of pharmaceuticals that target the same diseases that we are targeting. Smaller or earlier-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies.

There are a number of large pharmaceutical and biotechnology companies that are currently pursuing the development of products for the treatment of wet AMD and DME or have commercially approved products for the treatment of wet AMD or DME, including Roche, Regeneron and Novartis. The current standard of care for wet AMD is monotherapy administration of anti-VEGF-A therapies, including ranibizumab and aflibercept, as well as off-label use of bevacizumab. These drugs are well established therapies and are widely accepted by physicians, patients and third-party payors, which may make it difficult to convince these parties to switch to OPT-302 combination therapy. In addition to competition from other companies directly targeting wet AMD or DME, any products we may develop may also face competition from other types of therapies or patient and physician preferences. In addition, many companies are developing new therapeutics, and we cannot predict what the standard of care will be as OPT-302 or any future product candidates progress through clinical development.

If our competitors market products that are more effective, safer or cheaper than our products, that are more durable or have reduced injection burden compared to our products (including OPT-302), or that reach the market sooner than our products, we may not achieve commercial success. In addition, the biopharmaceutical industry is characterized by rapid technological change. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Technological advances or products developed by our competitors may render our technologies, products or product candidates obsolete, less competitive or not economical.

Many of our competitors have substantially greater financial, technical, human and other resources than we do and may be better equipped to develop, manufacture and market technologically superior products. In addition, many of these competitors have significantly longer operating histories and greater experience than we have in undertaking nonclinical studies and human clinical trials of new pharmaceutical products and in obtaining regulatory approvals of human therapeutic products. Clinical trials for the treatment of wet AMD and DME may be relatively costly and time consuming. The requirements for approval by the FDA and comparable non-U.S. regulatory authorities may change over time and this may require changes to ongoing or future clinical trial designs that could impact timelines and cost. Further, many of our competitors have established distribution channels for the commercialization of their products, whereas we have no such channel or capabilities. In addition, many competitors have greater name recognition and more extensive collaborative relationships.

As a result, our competitors may obtain regulatory approval of their products more rapidly than we do or may obtain patent protection or other intellectual property rights that limit our ability to develop or commercialize our product candidate or any future product candidates. Our competitors may also develop and succeed in obtaining approval for drugs that are more effective, more convenient, more widely used and less costly or have a better safety profile than our products and these competitors may also be more successful than we are in manufacturing and marketing their products. If we are unable to compete effectively against these companies, then we may not be able to commercialize our product candidate or any future product candidates or achieve a competitive position in the market. This would negatively affect our ability to generate revenue. Our competitors also compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and enrolling patients for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our inability to compete effectively in any of these aspects of our business could harm our business, financial condition, results of operations and prospects.

A fast track designation by the FDA for future product candidates, may not lead to a faster development or regulatory review or approval process and does not increase the likelihood that our product candidates will receive marketing approval.

If a drug or biologic is intended for the treatment of a serious or life-threatening condition and the product demonstrates the potential to address unmet medical needs for this condition, the sponsor may apply for FDA fast track designation for a particular indication. We may seek fast track designation for certain of our future product candidates, but there is no assurance that the FDA will grant this status to any of our future product candidates. If granted, fast track designation makes a product eligible for more frequent interactions with FDA to discuss the development plan and clinical trial design, as well as rolling review of the application, which means that the company can submit completed sections of its marketing application for review prior to completion of the entire submission. Marketing applications of products candidates with fast track designation may qualify for priority review under the policies and procedures offered by the FDA, but the fast track designation does not assure any such qualification or ultimate marketing approval by the FDA. The FDA has broad discretion whether or not to grant fast track designation, so even if we believe a particular product candidate is eligible for this designation, there can be no assurance that the FDA would decide to grant it. Even if we do receive fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a fast track designation does not provide any assurance of ultimate FDA approval. In addition, the FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program. In addition, the FDA may withdraw any fast track designation at any time.

OPT-302 and any future product candidates may not achieve adequate market acceptance among physicians, patients, healthcare payors and others in the medical community necessary for commercial success.

Even if our product candidates receive regulatory approval, they may not gain adequate market acceptance among physicians, patients, healthcare payors and others in the medical community. Given the number of drugs in development or currently approved for the treatment of wet AMD and DME, if we are unsuccessful in achieving a differentiated profile with OPT-302, including in combination with existing therapies, based on efficacy, safety and tolerability, dosing and administration, market acceptance will be limited. For example, current treatments for wet AMD, including ranibizumab, aflibercept and low cost, off-label use of bevacizumab, are well established in the medical community and perceived as demonstrating meaningful clinical response in many cases. As a result, doctors may continue to rely on these treatments without OPT-302 or may continue to use such existing treatments as first-line therapies. The medical community may also resist adopting a combination therapy over monotherapy for any of our targeted indications. In particular, recent clinical development has focused on maintaining vision gains with a VEGF-A inhibitor while reducing the number of injections. While we plan to evaluate the potential for co-formulation of OPT-302 with approved and/or biosimilar forms of VEGF-A inhibitors to provide flexibility of treatment options for physicians and to reduce the frequency and number of injections for patients, there can be no assurance that we will be successful or that any co-formulated product will have a favorable safety profile. If we are unable to reduce the injection burden of OPT-302 combination therapy or demonstrate sufficient efficacy improvements with a comparatively higher frequency and number of injections over standard of care anti-VEGF-A therapies, develop a co-formulation of OPT-302 for patients or otherwise increase the duration of efficacy of OPT-302 doses, or if physicians determine that a more frequent regimen is necessary, the market acceptance of OPT-302 may be limited which would harm our business, financial condition and results of operations.

In addition, the potential market opportunity for OPT-302 is difficult to estimate precisely. If OPT-302 receives marketing approval for the treatment of wet AMD, it will be approved solely for use in combination with one or more anti-VEGF-A therapies, and may be limited to use with only one anti-VEGF-A therapy for the treatment of wet AMD depending on whether the results from each of our Phase 3 clinical trials support an approved label for use of OPT-302 in combination with more than one anti-VEGF-A therapy. The market opportunity for OPT-302 will be dependent upon the continued use of anti-VEGF-A therapies in the treatment of wet AMD and the market share of such anti-VEGF-A therapies for which OPT-302 is approved as a combination therapy. The degree of market acceptance of any of our approved product candidates will depend on a number of factors, including:

- the efficacy, safety and dosing profile of the product candidate as demonstrated in clinical trials;
- the timing of market introduction of the product candidate as well as competitive products;
- the clinical indications for which the product candidate is approved;

- the imposition of a REMS which may include distribution or use restrictions;
- any restrictions on the use of our products to a subgroup of patients;
- acceptance of the product candidate as a safe and effective treatment by physicians and patients;
- the potential and perceived advantages of the product candidate over alternative treatments, including any similar generic treatments;
- the cost of treatment in relation to alternative treatments;
- the availability of coverage and adequate reimbursement and pricing by third parties and government authorities;
- patients' willingness to pay out-of-pocket in the absence of coverage and/or adequate reimbursement from third-party payors;
- the relative convenience and ease of administration;
- the frequency and severity of adverse events;
- the effectiveness of sales and marketing efforts; and
- unfavorable publicity relating to the product candidate.

Sales of medical products also depend on the willingness of physicians to prescribe the treatment, which is likely to be based on a determination by these physicians that the products are safe, therapeutically effective and cost effective. In addition, the inclusion or exclusion of products from treatment guidelines established by various physician groups and the viewpoints of influential physicians can affect the willingness of other physicians to prescribe the treatment. We cannot predict whether physicians, physicians' organizations, hospitals, other healthcare providers, government agencies or private insurers will determine that our products are safe, therapeutically effective and cost effective as compared with competing treatments.

Efforts to educate the medical community and third-party payors on the benefits of OPT-302 combination therapy may require significant resources and may not be successful. Demonstrating the safety and efficacy of our product candidates and obtaining regulatory approvals will not guarantee future revenue. Our commercial success also depends on coverage and adequate reimbursement of our product candidates by third-party payors, including government payors, which may be difficult or time-consuming to obtain, may be limited in scope and may not be obtained in all jurisdictions in which we may seek to market our products.

If the market opportunities for any product that we or our strategic collaborators develop are smaller than we believe they are, our revenue may be negatively affected and our business may suffer.

We intend to focus our product candidate development on therapies for the treatment of wet AMD and additional retinal disease indications such as DME or retinal vein occlusion, or RVO. Our projections of addressable patient populations that have the potential to benefit from treatment with our product candidate are based on estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. Additionally, the potentially addressable patient population for our product candidates may not ultimately be amenable to treatment with our product candidates. Our market opportunity may also be limited by future competitor treatments that enter the market. If any of our estimates are inaccurate, the market opportunities for any of our product candidates could be significantly diminished and have an adverse impact on our business.

If OPT-302 is approved by the FDA as a combination therapy for the treatment of wet AMD, the approval will be limited to this specific indication and, unless we seek regulatory approval for additional indications, we will be prohibited from marketing OPT-302 for other indications. We may be subject to fines, penalties or injunctions if we are determined to have promoted or be promoting the use of OPT-302 for unapproved or "off-label" uses, resulting in damage to our reputation and business.

If OPT-302 receives marketing approval for the treatment of wet AMD, it will be approved solely for use in combination with one or more anti-VEGF-A therapies, and may be limited to only one anti-VEGF-A therapy for the treatment of wet AMD depending on the results of our ongoing pivotal Phase 3 clinical trials. Although we are also developing OPT-302 for other retinal diseases, any regulatory approval of OPT-302 for wet AMD would not be cover the treatment of any other indication. As a result, we would be prohibited from promoting OPT-302 for the treatment of DME unless we are granted FDA approval for such indication.

The FDA strictly regulates the promotional claims that may be made about prescription products. While physicians may choose to prescribe products for uses that are not described in the product's labeling and for uses that differ from those tested in clinical trials and approved by the regulatory authorities, we are prohibited from marketing and promoting the products for indications that are not specifically approved by the FDA or comparable non-U.S. regulatory authorities. These "off-label" uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. Regulatory authorities in the United States generally do not restrict or regulate the behavior of physicians in their choice of treatment within the practice of medicine. Regulatory authorities do, however, restrict communications by biotechnology or pharmaceutical companies on off-label use. If the FDA determines that our promotional activities constitute promotion of an off-label use, it could request that we modify our promotional materials and subject us to FDA regulatory or enforcement actions as well as actions by other agencies, including issuance of warning letters or untitled letters, suspension or withdrawal of an approved product from the market, mandatory or voluntary recalls, civil fines, disgorgement of money, operating restrictions, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, injunctions or criminal prosecution, any of which could significantly harm our business.

OPT-302 is being developed to be used as a combination therapy for use with anti-VEGF-A therapies, which exposes us to additional risks.

We are developing OPT-302 to be used in combination with currently approved VEGF-A inhibitors. Even if OPT-302 were to receive marketing approval or be commercialized, we would continue to be subject to the risks that the FDA or similar regulatory authorities could revoke approval of some or all approved anti-VEGF-A therapies for safety, efficacy, manufacturing or supply issues. This could result in OPT-302 being restricted from commercialization or being less commercially successful.

We may also evaluate OPT-302 or any other future product candidates in combination with one or more other product candidates that have not yet been approved for marketing by the FDA or similar foreign regulatory authorities. We will not be able to market and sell OPT-302 or any product candidate we develop in combination with any such unapproved therapies that do not ultimately obtain marketing approval.

If the FDA or similar foreign regulatory authorities do not approve these other product candidates or revoke their approval of, or if safety, efficacy, manufacturing, or supply issues arise with, the drugs we choose to evaluate in combination with OPT-302 or any product candidate we develop, we may be unable to obtain approval of or market OPT-302 or any product candidate we develop.

If we fail to develop and commercialize additional product candidates, we may be unable to grow our business.

Although the development and commercialization of OPT-302 is currently our primary focus, as part of our longer-term growth strategy, we plan to evaluate the development and commercialization of other therapies related to retinal diseases. The success of this strategy depends primarily upon our ability to identify and validate new therapeutic candidates, and to identify, develop and commercialize new drugs and biologics. Our research efforts may initially show promise in discovering potential new drugs and biologics, yet fail to yield product candidates for clinical development for a number of reasons, including:

- we may need to rely on third parties to generate molecules for some of our product candidate programs;

- we may encounter product manufacturing difficulties that limit yield or produce undesirable characteristics that increase the cost of manufacturing our product candidates, cause delays or make our product candidates unmarketable;

- product candidates may cause adverse effects in patients or subjects, even after successful initial toxicology studies, which may make the product candidates unmarketable;

- product candidates may not demonstrate a meaningful benefit to patients or subjects; and

- our future collaboration partners may change their development profiles or plans for potential product candidates or abandon a therapeutic area or the development of a partnered product.

If any of these events occur, we may be forced to abandon our development efforts for one or more programs, which could harm our business, operating results and prospects and could potentially cause us to cease operations. Future research programs to identify new product candidates may 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.

Product candidates may require additional, time-consuming development efforts prior to commercial sale, including preclinical studies, clinical trials and approval by the FDA and/or comparable non-U.S. regulatory authorities. All product candidates are prone to the risks of failure that are inherent in pharmaceutical product development, including the possibility that the product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities. In addition, we cannot assure you that any such products that are approved will be manufactured or produced economically, be successfully commercialized, be widely accepted in the marketplace or be more effective than other commercially available alternatives.

Our business could be negatively affected by the effects of health epidemics, including the evolving effects of the COVID-19 pandemic, in regions where we or third parties on which we rely have significant manufacturing facilities, concentrations of clinical trial sites or other business operations.

Health epidemics in regions where we have concentrations of clinical trial sites or other business operations could negatively affect our business, including by causing significant disruption in the operations of third-party manufacturers and CROs upon whom we rely. For example, the novel coronavirus disease 2019, or COVID-19, pandemic has presented a substantial public health and economic challenge around the world and continues to affect employees, patients, communities and business operations, as well as the U.S. economy and financial markets, despite the availability of FDA-approved vaccines against COVID-19.

Based on guidance issued by Australian federal and state governments, we transitioned to a remote work environment for all of our employees. In connection with these measures, we may be subject to claims based upon, arising out of, or related to COVID-19 and our actions and responses thereto, including any determinations that we may make to continue to operate or to re-open our facilities. Further, the effects of the continued shelter-in-place orders in Australia and across the world and our work-from-home policies may negatively impact productivity, disrupt our business and delay our clinical programs and timelines, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course. These and similar, and perhaps more severe, disruptions in our operations could negatively impact our business, financial condition, results of operations and growth prospects. As the pandemic continues, we may experience a negative impact on our ability to initiate clinical trial sites, maintain patient enrollment and enroll new patients which may impact timelines in the future. Our ability to attract additional clinical trial sites and principal investigators to conduct our clinical trials and to conduct the necessary clinical trial site initiation procedures may be impacted by quarantines, shelter-in-place and similar restrictions imposed by federal, state and local governments. These restrictions may also prohibit patients from enrolling in, or continuing to participate in, our clinical trials. Principal investigators and clinical trial site staff, as healthcare providers, may have heightened exposure to COVID-19. While none of the patients in our ongoing clinical trials have discontinued due to COVID-19, certain of our patients have contracted COVID-19, and further health impacts from COVID-19 on our patients, clinical trial site staff or principal investigators could negatively impact the conduct of our clinical trials at their sites Similarly, potential participants in our clinical trials, many of whom are medically vulnerable, may be unwilling to enroll in, and enrolled patients may be unwilling to continue to participate in, our clinical trials due to an unwillingness to travel to sites for required screening and clinical trial visits and procedures. Enrolled patients may be unable to comply with clinical trial protocols if quarantines, shelter-in-place and similar restrictions continue to impede patient movement or interrupt healthcare services. In

addition, we may be required to develop and implement additional clinical study policies and procedures designed to help protect patients from the COVID-19 disease, which may include using telemedicine visits, remote monitoring of patients and clinical trial sites, and measures designed to ensure that data from clinical trials that may be disrupted as result of the pandemic are collected pursuant to the study protocol and consistent with Good Clinical Practice, or GCP, with any significant protocol deviation reviewed and approved by the clinical trial site institutional review board, or IRB, all or any of which could materially and negatively affect our clinical development timelines and our ability to obtain regulatory approvals of our product candidates, and could significantly increase our costs. We could also see an impact on our ability to report clinical trial results, or interact with regulators, ethics committees or other important agencies due to limitations in regulatory authority employee resources or otherwise. In addition, the FDA or comparable non-U.S. regulatory authorities may refuse to accept data from clinical trials conducted in geographies experiencing heightened impact from COVID-19.

Moreover, we rely on third-party CROs and other third parties to assist us with clinical development activities, and we cannot guarantee that they will continue to perform their contractual duties in a timely and satisfactory manner as a result of the COVID-19 pandemic. In addition, quarantines, shelter-in-place and similar government orders could impact personnel at third-party manufacturing facilities in the United States and other countries, or the availability or cost of materials, which would disrupt our supply chain. In particular, some of our suppliers of certain materials used in the production of our drug products are located in Europe. In any event, if the COVID-19 pandemic continues and persists for an extended period of time or more acutely impacts geographies with particular impact on our business, we could experience significant disruptions to our clinical development timelines, which would harm our business, financial condition, results of operations and growth prospects.

In addition, while the potential economic impact brought by, and the duration of, the COVID-19 pandemic may be difficult to assess or predict, the pandemic could result in significant and prolonged disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could harm our business and the value of our ordinary shares and ADSs.

Risks Related to Legal and Regulatory Compliance Matters

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

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, statutory, regulatory and policy changes, and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, in recent years, including in 2018 and 2019, the U.S. government shut down several times and certain regulatory agencies, such as the FDA, had to furlough critical employees and stop critical activities. Separately, in response to the COVID-19 pandemic, in March 2020, the FDA announced its intention to postpone most inspections of foreign manufacturing facilities and products through April 2020. Also in March 2020, the FDA announced its intention to temporarily postpone routine surveillance inspections of domestic manufacturing facilities. FDA has continued, on a case-by-case basis, to conduct mission-critical inspections and other activities to ensure that FDA-regulated pharmaceutical products are meeting applicable FDA requirements. In July 2020, FDA resumed prioritized domestic inspections. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic or issue guidance materially affecting the conduct of clinical trials. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews or other regulatory activities, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, in our operations as

a public company, future government shutdowns or delays could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Even if we commercialize OPT-302 or any future product candidate, we may face challenges to achieving profitability such as our products becoming subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which could harm our business.

In the United States and in other countries, patients who are prescribed treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. The availability of coverage and adequacy of reimbursement for our products by third-party payors, including government health care programs (e.g., Medicare, Medicaid, TRICARE), managed care providers, private health insurers, health maintenance organizations and other organizations is essential for most patients to be able to afford medical services and pharmaceutical products such as OPT-302 or any our product candidates. Third-party payors decide which medications they will pay for and establish reimbursement levels. The availability of coverage and extent of reimbursement by governmental and other third-party payors is essential for most patients to be able to afford treatments such as OPT-302.

In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, or HHS. CMS decides whether and to what extent our products will be covered and reimbursed under Medicare and private payors tend to follow CMS to a substantial degree. Other countries have equivalent authorities who play a similar role. Factors payors consider in determining reimbursement are based on whether the product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Our ability to commercialize any products successfully will depend in part on the extent to which coverage and adequate reimbursement for these products and related treatments will be available from third-party payors, including government health care programs and private health insurers. Moreover, a payor’s decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. If coverage and adequate reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

In the United States, no uniform policy for coverage and reimbursement for products exists among third-party payors. Therefore, coverage and reimbursement for our products can differ significantly from payor to payor. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. One payor’s determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product. Third-party payors may also limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication.

Government authorities and other third-party payors in the United States and abroad have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications and for newly approved products, and as a result, they may not cover or provide adequate reimbursement for OPT-302 and future product candidates. Increasingly, certain third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that coverage and reimbursement will be available for any product that we or our future collaborators commercialize and, if reimbursement is available, what the level of reimbursement will be. Coverage and reimbursement may impact the demand for, or the price of, any product candidate for which we or our future

collaborators obtain marketing approval. If coverage and reimbursement are not available or reimbursement is available only to limited levels, we and our future collaborators may not be able to successfully commercialize any product candidate for which marketing approval is obtained. A decision by a third-party payor not to cover or not to separately reimburse for our medical products or therapies using our products could reduce physician utilization of our products once approved. Assuming there is coverage for our product candidates, or therapies using our product candidates by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. We cannot be sure that coverage and reimbursement in the United States will be available for OPT-302 and any future product candidates and any reimbursement that may become available may not be adequate or may be decreased or eliminated in the future.

There may be significant delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the drug is approved by the FDA or comparable non-U.S. regulatory authorities. Moreover, eligibility for coverage and reimbursement does not imply that a drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may only be temporary. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Our inability to promptly obtain coverage and profitable reimbursement rates from both government-funded and private payors for any approved products that we develop could harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

The regulations that govern marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some non-U.S. markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay or limit our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenue we generate from the sale of the product in that particular country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

To become and remain profitable, we or any potential future collaborator must develop and eventually commercialize OPT-302 or any future product candidates with significant market potential at an adequate profit margin after cost of goods sold and other expenses. Commercialization of OPT-302 or any future product candidates may entail a substantial cost of goods sold and there can be no assurance that we will be able to achieve a suitable gross margin with respect to sales of OPT-302 or any future product candidates.

Changes in U.S. healthcare law and implementing regulations, as well as changes in healthcare policy, and equivalent changes in the laws and policies in other countries may impact our business in ways that we cannot currently predict and may harm our business and results of operations.

There have been, and likely will continue to be, several executive, legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. Among policy makers and payors in the United States there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access and the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to as the Affordable Care Act, substantially changed the way healthcare is financed by both the government and private insurers, and significantly impacts the U.S. pharmaceutical industry. The Affordable Care Act, among other things: (1) introduced a new average manufacturer price definition for drugs and biologics that are inhaled, infused, instilled, implanted or injected and not generally dispensed through retail community pharmacies; (2) increased the minimum Medicaid rebates owed by manufacturers under the

Medicaid Drug Rebate Program and expanded rebate liability from fee-for-service Medicaid utilization to include the utilization of Medicaid managed care organizations as well; (3) established a branded prescription drug fee that pharmaceutical manufacturers of branded prescription drugs must pay to the federal government; (4) expanded the list of covered entities eligible to participate in the 340B drug pricing program by adding new entities eligible for the program; (5) established a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018, or BBA, effective as of January 2019) point-of-sale discounts off negotiated prices of applicable branded drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; (6) extended manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations; (7) expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals, including individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability; (8) created a licensure framework for follow-on biologic products; and (9) established a Center for Medicare and Medicaid Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

Since its enactment, there have been executive, judicial and Congressional challenges to certain aspects of the Affordable Care Act. For example, the Tax Cuts and Jobs Act of 2017, or the TCJA, was enacted, which included a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the Affordable Care Act on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas ruled that the individual mandate is a critical and inseverable feature of the Affordable Care Act, and therefore, because it was repealed as part of the TCJA, the remaining provisions of the Affordable Care Act are invalid as well. On December 18, 2019, the U.S. Court of Appeals for the 5th Circuit ruled that the individual mandate was unconstitutional but remanded the case back to the District Court to determine whether the remaining provisions of the Affordable Care Act are invalid as well. On June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the Affordable Care Act will remain in effect in its current form. It is possible that the Affordable Care Act will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the Affordable Care Act.

Other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year pursuant to the Budget Control Act of 2011 and subsequent laws, which began in 2013 and will remain in effect through 2030, unless additional Congressional action is taken. These Medicare sequester reductions have been suspended from May 1, 2020 through December 31, 2021 due to the COVID-19 pandemic. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. New laws may result in additional reductions in Medicare and other healthcare funding, which may materially negatively affect customer demand and affordability for our products and, accordingly, the results of our financial operations.

Also, there has been heightened governmental scrutiny recently over the manner in which pharmaceutical companies set prices for their marketed products, which have resulted in several Congressional inquiries and proposed federal legislation, as well as state efforts, designed to, among other things, bring more transparency to product pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. At the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that seek to implement several of the administration's proposals. As a result, the FDA released a final rule on September 24, 2020, effective November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Medicare Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit

managers and manufacturers, the implementation of which have also been delayed until January 1, 2023. On November 20, 2020, CMS issued an interim final rule implementing the Trump administration's Most Favored Nation executive order to tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries. As a result of litigation challenging the Most Favored Nation model, on August 10, 2021, CMS published a proposed rule that seeks to rescind the Most Favored Nation Model interim final rule. Additionally, based on a recent executive order, the Biden administration expressed its intent to pursue certain policy initiatives to reduce drug prices. At the state level, individual states in the United States are increasingly active in 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. Legally mandated price controls on payment amounts by third-party payors or other restrictions on coverage or access could harm our business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our product candidates that we successfully commercialize or put pressure on our product pricing.

We expect that these and other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and lower reimbursement, and put additional downward pressure on the price that we receive for any approved product. It is possible that additional governmental action is taken in response to the COVID-19 pandemic. Any reduction in reimbursement from Medicare or other government-funded programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs, once marketing approval is obtained. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action in the United States. If we or any third parties we may engage are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, our product candidates may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

As a company primarily based outside of the United States, our business is subject to economic, political, regulatory and other risks associated with international operations.

As a company with substantial operations in Australia and an international clinical trial program, our business is subject to risks associated with conducting business outside the United States. Many of our suppliers and clinical trial relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including:

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing and changing regulatory requirements for product approvals;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates, Australian dollar, U.S. dollar, euro and currency controls;
- changes in a specific country's or region's political or economic environment;
- trade protection measures, import or export licensing requirements or other restrictive actions by governments;

- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, health epidemics, or natural disasters including earthquakes, typhoons, floods and fires.

If we fail to comply with non-U.S. regulatory requirements governing human clinical trials and marketing approval for drugs, we could be prevented from selling our product candidates in non-U.S. markets, which may negatively affect our operating results and financial condition.

The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement for marketing our product candidates outside the United States vary greatly from country to country and may require additional testing. We expect that our future clinical development of our product candidates will involve a number of clinical trials in non-U.S. jurisdictions. We have no direct experience as a company in obtaining non-U.S. regulatory approvals. The time required to obtain approvals outside the United States may differ from that required to obtain FDA approval. We may not obtain non-U.S. regulatory approvals on a timely basis, if at all. Approval by the FDA does not guarantee approval by comparable non-U.S. regulatory authorities, and approval by one non-U.S. regulatory authority does not ensure approval by regulatory authorities in other countries or by the FDA. Failure to comply with these regulatory requirements or obtain required approvals could impair our ability to develop non-U.S. markets for our product candidates and may harm our results of operations and financial condition.

Price controls may be imposed in non-U.S. markets, which may negatively affect our future profitability.

In some countries, particularly EU member states, Japan, Australia and Canada, the pricing of prescription drugs is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU member states and parallel distribution, or arbitrage between low-priced and high-priced member states, can further reduce prices. In some countries, we or our collaborators may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidates to other available therapies in order to obtain or maintain reimbursement or pricing approval. Publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business, revenues or profitability could be harmed.

We have received tax incentives under the Research and Development Tax Incentive scheme in Australia that may become repayable if we did not or do not comply with the rules of the scheme, or we may become ineligible for tax incentives in our current or future tax years, which could harm our business, financial condition and results of operations.

We have received cash incentives in the past under the Research and Development Tax Incentive scheme, or the R&D Scheme, to offset the costs of our clinical trials and other qualifying expenses incurred both in Australia and other jurisdictions. Certain research and development costs that we incur in the future may be ineligible for

cash incentives under the R&D Scheme. For example, costs incurred outside Australia in connection with our future clinical trials are generally not eligible for cash incentives under the R&D Scheme. In addition, the federal government of Australia and the Australian Taxation Office, or ATO, could change the rules of the regulatory regime or amend past tax returns and, as a result, amounts paid to us may become repayable to the ATO including the amount of tax incentives in respect of our fiscal year ended June 30, 2021 included as current receivables in our consolidated financial statements. We have received an aggregate of US$28.5 million (A$40.5 million) in cash tax incentives during the five fiscal years ended June 30, 2021 under the R&D Scheme. As of June 30, 2021, our current tax receivable under the R&D Scheme was US$5.0 million. This receivable amount as of June 30, 2021 is based on Australian legislation as enacted as of June 30, 2021. Any proposed changes to the legislation, such as rate changes to eligibility requirements, may have a retrospective impact on our current tax receivable under the R&D Scheme, currently no such legislative changes have occurred. Any rule changes made to reduce the amount we are able to claim under the R&D Scheme currently or in the future and any retrospective changes made to the R&D Scheme that reduce the incentives that we have claimed in past tax years could harm our business, financial condition and results of operations.

The withdrawal of the United Kingdom, or the U.K., from the European Union, or the E.U., commonly referred to as "Brexit", may adversely impact our ability to obtain regulatory approvals of our product candidates in the U.K. or the EU and may require us to incur additional expenses to develop and commercialize our product candidates in the U.K. or the EU or receive clinical supply of our product candidates from manufacturing partners in the U.K.

Following the result of a referendum in 2016, the U.K. left the E.U. on January 31, 2020, commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed between the U.K. and the E.U., the U.K. was subject to a transition period until December 31, 2020 (the "Transition Period"), during which E.U. rules continued to apply. A trade and cooperation agreement (the "Trade and Cooperation Agreement") that outlines the future trading relationship between the United Kingdom and the European Union was agreed in December 2020.

Since a significant proportion of the regulatory framework in the U.K. applicable to our business and our product candidate 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, approval and commercialization of our product candidate in the U.K. or the EU. For example, 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 candidate in Great Britain. It is currently unclear whether the Medicines & Healthcare products Regulatory Agency in the U.K. is sufficiently prepared to handle the increased volume of marketing authorization applications that it is likely to receive. Any delay in obtaining, or an inability to obtain, any marketing approvals, would delay or prevent us from commercializing our product candidate in the U.K. or the E.U. 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 U.K. and the E.U. there may be additional non-tariff costs to such trade which did not exist prior to the end of the Transition Period. Further, should the U.K. diverge from the E.U. from a regulatory perspective in relation to medicinal products, tariffs could be put into place in the future. 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 U.K. It is also possible that Brexit may negatively affect our ability to attract and retain employees, particularly those from the E.U.

Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercialize any resulting products. Product liability claims may be brought against us by subjects enrolled in our clinical trials, patients, or others using our products. If we cannot successfully defend ourselves against claims that our product candidates or products that we may develop

caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or products that we may develop;
- product recalls or a change in the indications for which products may be used;
- termination of clinical trial sites or entire trial programs;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial subjects or patients;
- loss of revenue;
- diversion of management and scientific resources from our business operations; and
- the inability to commercialize any products that we may develop.

Our clinical trial liability insurance coverage may not adequately cover all liabilities that we may incur. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. Our inability to obtain product liability insurance at an acceptable cost or to otherwise protect against potential product liability claims could prevent or delay the commercialization of any products or product candidates that we develop. We intend to expand our insurance coverage for products to include the sale of commercial products if we obtain marketing approval for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. If we are sued for any injury caused by our products, product candidates or processes, our liability could exceed our product liability insurance coverage and our total assets. Claims against us, regardless of their merit or potential outcome, may also generate negative publicity or harm our ability to obtain physician endorsement of our products or expand our business.

Our business operations and relationships with investigators, healthcare professionals, consultants, third-party payors, patient organizations and customers are subject to broadly applicable healthcare laws and regulations, which could expose us civil to penalties, criminal sanctions, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers and third-party payors will play a primary role in the recommendation and prescription of any product candidate for which we obtain regulatory approval. Our current and future arrangements may expose us to broadly applicable fraud and abuse and other healthcare laws that may constrain the business or financial arrangements and relationships through which we would market, sell and distribute our products. In particular, the research of our product candidates, as well as the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, structuring and commission(s), certain customer incentive programs and other business or financial arrangements.

Such laws include, but are not limited to, the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration (including any kickback, bribe or rebate), directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid. The term “remuneration” has been broadly interpreted to

include anything of value. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. The Anti-Kickback Statute has been interpreted to apply to arrangements between biopharmaceutical manufacturers, on the one hand, and prescribers, purchasers and formulary managers, among others, on the other. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;

- the federal criminal and civil false claims laws, including the False Claims Act, which can be enforced through civil whistleblower or qui tam actions, which imposes criminal and civil penalties, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent, knowingly making, using or causing to be made or used, a false record or statement material to a false or fraudulent claim, or knowingly making or causing to be made, a false statement to avoid, decrease or conceal an obligation to pay money to the federal government. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false or fraudulent statements relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, which also impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information on health plans, health care clearing houses, and certain healthcare providers and their business associates, defined as independent contractors or agents of covered entities that create, receive or obtain protected health information in connection with providing a service for or on behalf of a covered entity, as well as their covered subcontractors. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys’ fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personally identifiable information, or personal information or personal data, in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts;

- the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program (with certain exceptions) to report annually to the government information related to payments or other “transfers of value” made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, and requires applicable manufacturers and group purchasing organizations to report annually to the ownership and investment interests held by such physicians and their immediate family members and payments or other “transfers of value” to such physicians (covered manufacturers are required to submit reports to CMS by the 90th day of each calendar year). Effective January 1, 2022, applicable manufacturers will also be required to report payments and other transfers of value made in the previous year to certain non-physician providers, including physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists and certified nurse midwives; and

- analogous state and non-U.S. laws and regulations, such as state anti-kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, or otherwise restrict payments that may be made to healthcare providers or other interactions with healthcare providers and other potential referral

sources; and state or non-U.S. laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the national or federal government, and state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures or drug pricing; and state, non-U.S., and local laws that require the registration of pharmaceutical sales representatives; and state and non-U.S. laws governing the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Pharmaceutical and other healthcare companies have been prosecuted under these laws for a variety of promotional and marketing activities, such as: providing free trips, free or discounted goods, improper consulting fees and grants and other monetary benefits to prescribers; reporting to pricing services inflated average wholesale prices that were then used by federal programs to set reimbursement rates; engaging in off-label promotion; and submitting inflated best price information to the Medicaid Rebate Program to reduce liability for Medicaid rebates. Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If any actions are instituted against us for violation of these laws or regulations, and we are not successful in defending ourselves, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative sanctions, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, imprisonment, integrity oversight and reporting obligations, contractual damages, reputational harm, diminished profits and future earnings, and curtailment or restructuring of our operations, any of which could harm our ability to operate our business and our results of operations.

The global data protection landscape is rapidly evolving, and we may be affected by or subject to new, amended or existing laws and regulations in the future, including as our operations continue to expand or if we operate in non-U.S. jurisdictions. Several non-U.S. jurisdictions, including the European Union, or EU, its member states, the United Kingdom, Japan and Australia, among others, have adopted legislation and regulations that increase or change the requirements governing the collection, use, disclosure and transfer of the personal information of individuals in these jurisdictions and have established procedures for the imposition of substantial penalties for failure to comply with related obligations. Additionally, certain countries have passed or are considering passing laws that require local data residency and/or restrict the international transfer of data and/or impose data localization requirements with respect to certain personal information. These laws have the potential to increase costs of compliance, risks of noncompliance and penalties for noncompliance.

European data collection is governed by restrictive regulations governing the collection, use, processing and cross-border transfer of personal information.

We may collect, process, use or transfer personal information from individuals located in the European Economic Area in connection with our business, including in connection with conducting clinical trials in the European Economic Area, or the EEA. Additionally, if any of our product candidates are approved, we may seek to commercialize those products in the European Economic Area. The collection and use of personal health data in the European Economic Area is governed by the provisions of the General Data Protection Regulation ((EU) 2016/679), or the GDPR, along with other European Union and country-specific laws and regulations. The GDPR has "extra-territorial" reach in that it applies to any processing of personal data that concerns the offering of goods or services to individuals in the EEA or U.K. (as applicable) and the monitoring of their behavior, regardless of the existence of an establishment in the EEA or U.K. (as applicable). As such, the GDPR applies to our clinical trials and other operations taking in place in the EEA and U.K.

The GDPR sets out a number of requirements that must be complied with when handling personal data, including: the obligation to appoint a data protection officer in certain circumstances; increased accountability and record-keeping obligations; increased transparency obligations for data controllers; onerous obligations on service providers who process personal data on our behalf; the obligation to carry out so-called data protection impact assessments in certain circumstances; obligations to comply with data subjects' exercise of an increased set of rights in certain circumstances; a heightened and more codified standard of data subject consent; and the obligation to notify certain significant personal data breaches to the relevant supervisory authorities and affected individuals. In addition, the GDPR materially expands the definition of what is expressly provided to constitute personal data (including, for example, by clarifying that the GDPR applies to "pseudonymized" (key-coded) data,

which is often processed by sponsors in the context of clinical trials where identification of underlying subjects is not required). As such, the GDPR is likely to increase the compliance burden on us, including by mandating potentially burdensome documentation requirements and granting certain rights to individuals to control how we collect, use, disclose, retain and leverage information about them. The processing of sensitive personal data, such as physical health conditions, may impose heightened compliance burdens under the GDPR and is a topic of active interest among foreign regulators. In addition, the GDPR provides for breach reporting requirements, more robust regulatory enforcement and fines of up to 20 million euros (and/or in respect of the UK GDPR, 17.5 million pounds sterling) or up to 4% of annual global revenue (whichever is higher). While the GDPR affords some flexibility in determining how to comply with the various requirements, significant effort and expense has been, and will continue to be, invested to ensure continuing compliance.

Moreover, the requirements under the GDPR may change periodically. The GDPR also provides that member states may make their own national laws and regulations to introduce specific requirements related to the processing of "special categories of personal data", which includes health-related personal data. In the U.K., the Data Protection Act 2018 complements the UK GDPR in this regard. This may lead to greater divergence in the application, interpretation and enforcement of the law that applies to the processing of personal data across the EEA and/or U.K., compliance with which, as and where applicable, may increase our costs and could increase our overall compliance risk. Such country-specific regulations could also limit our ability to collect, use and share data in the context of our EEA and/or U.K. operations, and/or could cause our compliance costs to increase, ultimately having an adverse impact on our business and harming our business and financial condition.

In addition, the GDPR prohibits the transfer of personal data from the EEA, U.K. and Switzerland to the U.S. and other countries in respect of which the European Commission or other relevant regulatory body has not issued a so-called "adequacy decision" (known as "third countries"), unless the parties to the transfer have implemented specific safeguards to protect the transferred personal data. One of the primary safeguards used for transfers of personal data to the U.S. was the EU-U.S. Privacy Shield framework administered by the U.S. Department of Commerce. However, certain recent EU court decisions cast doubt on the ability to use one of the primary alternatives to the EU-U.S. Privacy Shield and Swiss-U.S. Privacy Shield, namely the European Commission's Standard Contractual Clauses, to lawfully transfer personal data to the U.S. and other third countries. In addition, the European Commission has recently published new versions of the Standard Contractual Clauses, which must be used for all new transfers of personal data from the EEA to third countries (including the United States) starting in September 2021, and all existing transfers of personal data from the EEA to third countries relying on the existing versions of the Standard Contractual Clauses must be replaced by December 2022. The implementation of the new Standard Contractual Clauses will necessitate significant contractual overhaul of our data transfer arrangements with customers, sub-processors and vendors. Use of both the existing and the new Standard Contractual Clauses must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals, and additional supplementary technical, organizational and/or contractual measures and/or contractual provisions may need to be put in place.

At present, there are few if any viable alternatives to the Standard Contractual Clauses, and there remains some uncertainty with respect to the nature and efficacy of such supplementary measures in ensuring an adequate level of protection of personal data. As such, transfers of personal data from the EEA and the U.K. to the U.S. and other third countries may not fully comply with the cross-border data transfer restrictions set out in the GDPR. As supervisory authorities issue further guidance on personal data export mechanisms (including circumstances where the Standard Contractual Clauses can and cannot be used) and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines. In addition, if we are unable to transfer personal data between and among countries and regions in which we operate and/or engage providers and/or otherwise transfer personal data, this could affect the manner in which we receive and/or provide our services, the geographical location or segregation of our relevant systems and operations and could adversely affect our financial results and generally increase compliance risk as a result. Additionally, other countries outside of Europe have enacted or are considering enacting similar cross-border data transfer restrictions and laws requiring local data residency, which could increase the cost and complexity of operating our business.

Furthermore, following Brexit, the relationship between the U.K. and the EEA in relation to certain aspects of data protection law remains somewhat uncertain. In June 2021, the European Commission issued an adequacy decision under the GDPR which allows transfers (other than those carried out for the purposes of U.K. immigration control) of personal data from the EEA to the U.K. to continue without restriction for a period of four years. After that period, the adequacy decision may be renewed only if the U.K. continues to ensure an adequate level of data protection. During these four years, the European Commission will continue to monitor the legal situation in the

U.K. and could intervene at any point if the U.K. deviates from the level of data protection in place at the time of issuance of the adequacy decision. If the adequacy decision is withdrawn or not renewed, transfers of personal data from the EEA to the U.K. will require a valid "transfer mechanism" and we may be required to implement new processes and put new agreements in place, such as Standard Contractual Clauses, to enable transfers of personal data from the EEA to the U.K. to continue, which could disrupt our operations.

In addition, while the U.K. data protection regime currently permits data transfers from the U.K. to the EEA and other third countries covered by a European Commission adequacy decision, and currently includes a framework to permit the continued use of the existing version of the Standard Contractual Clauses for personal data transfers from the U.K. to third countries, this is subject to change in the future, and any such changes could have implications for our transfers of personal data from the U.K. to the EEA and other third countries. In particular, the U.K. Information Commissioner's Office has stated that it is working on its own bespoke version of the Standard Contractual Clauses and it is not clear whether the new Standard Contractual Clauses published by the European Commission will be accepted as a valid mechanism to permit the transfer of personal data from the U.K. to third countries and/or whether any U.K. version of the Standard Contractual Clauses will supersede the existing and/or new EU version of the Standard Contractual Clauses. This could necessitate the implementation of both U.K. and EU versions of Standard Contractual Clauses, which would require significant resources and result in significant cost to implement and manage.

Any failure or perceived failure by us to comply with federal, state, or foreign laws or self-regulatory standards could result in negative publicity, diversion of management time and effort and proceedings against us by governmental entities or others. In many jurisdictions, enforcement actions and consequences for noncompliance are rising. As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business.

If we are not able to obtain required regulatory approvals, we will not be able to commercialize OPT-302 or any future product candidate, and our ability to generate product revenue will be impaired.

OPT-302 and any future product candidate that we may develop, as well as the activities associated with their development and commercialization, including their design, research, testing, manufacture, safety, efficacy, recordkeeping, labeling, packaging, storage, approval, advertising, promotion, sale and distribution are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by similar regulatory authorities outside the United States. Failure to obtain marketing approval for, and thus commercialize any product candidate, could negatively impact our ability to generate any revenue from product sales.

We have not received approval from regulatory authorities to market any product candidate in any jurisdiction, and it is possible that our product candidate will never obtain the appropriate regulatory approvals necessary for us to commence product sales. Neither we nor any collaborator is permitted to market our product candidate in the United States or any other jurisdiction until we receive regulatory approval of a BLA from the FDA or similar application from regulatory authorities outside of the United States.

The time required to obtain approval of a BLA by the FDA or similar application from regulatory authorities outside of the United States is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authority. Prior to submitting a BLA to the FDA or any comparable application to any other non-U.S. regulatory authorities for approval of any product candidate, we will need to complete pivotal Phase 3 clinical trials and demonstrate favorable results with respect to safety, tolerability and efficacy. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions.

Securing marketing approvals requires the submission of extensive nonclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the safety and efficacy of our product candidate for the specified indications. We expect to rely on third-party CROs, consultants and our collaborators to assist us in filing and supporting the applications necessary to gain marketing approvals. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, regulatory authorities. Errors in the submission of applications for marketing approval or issues, including those related to gathering the appropriate data and the inspection process, may ultimately delay or affect our ability to obtain regulatory approval, commercialize our product candidate and generate product revenue.

Our failure to obtain regulatory approval in international jurisdictions would prevent us from marketing our product candidates outside the United States.

If we succeed in developing any products, we intend to market them in non-U.S. jurisdictions in addition to the United States. In order to market and sell our products in other jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. We may not obtain non-U.S. regulatory approvals on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions. Approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. If we fail to obtain approval of any of our product candidates by regulatory authorities in another country, we will be unable to commercialize our product in that country, and the commercial prospects of that product candidate and our business prospects could decline. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, we must secure product reimbursement approvals before regulatory authorities will approve the product for sale in that country. Obtaining non-U.S. regulatory approvals and compliance with non-U.S. regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries and regulatory approval in one country does not ensure approval in any other country, while a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory approval process in others. Also, regulatory approval for any of our product candidates may be withdrawn if we fail to comply with regulatory requirements, if problems occur after the product candidate reaches the market or for other reasons. If we fail to comply with the regulatory requirements in international markets and fail to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business will be negatively affected.

Even if OPT-302 combination therapy or any future product candidate receives regulatory approval, it may still face future development and regulatory difficulties.

Even if we obtained regulatory approval for a product candidate, it would be subject to ongoing requirements by the FDA and comparable non-U.S. regulatory authorities governing the manufacture, quality control, further development, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, recordkeeping and reporting of safety and other post-market information. The FDA and comparable non-U.S. regulatory authorities will continue to closely monitor the safety profile of any product even after approval. If the FDA, or comparable non-U.S. regulatory authorities, become aware of new safety information after approval of any of our product candidates, it may require labeling changes or establishment of a risk evaluation and mitigation strategy or similar strategy, impose significant restrictions on a product's indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies or post-market surveillance.

In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practices, or cGMP, regulations and standards. If we or a regulatory agency discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. If we, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, or undesirable side effects caused by such products are identified, a regulatory agency may:

- issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings about such product;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- revise labeling, including adding limitations on approved uses or the additions of additional warnings, contraindications or other safety information including boxed warnings;

- impose a REMS which may include distribution on or use restrictions;
- require that we conduct post-marketing studies;
- require us to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend marketing of, withdraw regulatory approval of or recall such product;
- suspend any ongoing clinical studies;
- refuse to approve pending applications or supplements to applications filed by us;
- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products, refuse to permit the import or export of products or require us to initiate a product recall.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our products and generate product revenue.

Advertising and promotion of any product candidate that obtains approval in the United States will be heavily scrutinized by the FDA, the Department of Justice, the Department of Health and Human Services' Office of Inspector General, state attorneys general, members of Congress and the public. Violations, including promotion of our products for unapproved (or off-label) uses, are subject to enforcement letters, inquiries and investigations and significant civil and criminal sanctions by the government. In the United States, engaging in the impermissible promotion of our products for off-label uses can also subject us to false claims litigation under federal and state statutes, which can lead to significant civil and criminal penalties. Additionally, comparable non-U.S. regulatory authorities will heavily scrutinize advertising and promotion of any product candidate that obtains approval outside of the United States.

The FDA's policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would negatively affect our business, prospects and ability to achieve or sustain profitability.

Risks Related to Our Reliance on Third Parties

We have relied on, and expect to continue to rely on, third-party manufacturers to produce OPT-302 or any future product candidates. Any failure by a third-party manufacturer to produce acceptable product candidates for us pursuant to our specifications and regulatory standards may delay or impair our ability to initiate or complete our clinical trials, obtain and maintain regulatory approvals or commercialize approved products.

The manufacturing of biologic drugs such as OPT-302 is complex and the process of identifying the qualifying suppliers takes a significant investment of time and money. We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates, and we lack the resources and the capabilities to do so. As a result, we currently rely, and expect to rely for the foreseeable future, on third-party manufacturers to supply us with OPT-302 and any future product candidates.

We currently have a sole source relationship with Patheon N.V., a division of Thermo Fisher Scientific Inc., pursuant to which they supply us with OPT-302 drug substance and drug product. If there should be any disruption in our supply arrangement with Patheon, including any adverse events affecting Patheon or Thermo Fisher Scientific, it could have a negative effect on the clinical development of OPT-302 and other operations while we work to identify and qualify an alternate supply source. In addition, we do not have a long-term supply arrangement to purchase anti-VEGF-A therapy for use in combination with OPT-302 in our clinical trials and acquire such drug product on a purchase order basis. Any complications with our existing suppliers of anti-VEGF-

A therapies could considerably delay our clinical trials for OPT-302, including our Phase 3 pivotal clinical program of OPT-302 for the treatment of wet AMD, or the regulatory approvals of OPT-302.

Reliance on third-party suppliers and manufacturers entails risks to which we would not be subject if we manufacture product candidates or products ourselves. For example, if we do not maintain our key manufacturing relationships, including with Patheon, we may fail to find replacement manufacturers or develop our own manufacturing capabilities in a timely manner or at all, which could delay or impair our ability to obtain regulatory approval for our products and substantially increase our costs or deplete profit margins, if any. If we do find replacement manufacturers, we may not be able to enter into agreements with them on terms and conditions favorable to us in a timely manner, if at all, and there could be a substantial delay before new facilities could be qualified and registered with or licensed by the FDA and other comparable non-U.S. regulatory authorities.

Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- failure of the third party to manufacture product candidates according to our schedule, or at all, including if our third-party contractors give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreements between us and them;
- breach of the manufacturing agreement by the third party because of factors beyond our control (including a failure to manufacture product candidates in accordance with our product specifications);
- the failure of the third-party manufacturer to comply with applicable regulatory requirements and reliance on third-parties for manufacturing process development, regulatory compliance and quality assurance;
- mislabeling of clinical supplies, potentially resulting in the wrong dose amounts being supplied or active drug or placebo not being properly identified;
- clinical supplies not being delivered to clinical sites on time, leading to clinical trial interruptions, or of drug supplies not being distributed to commercial vendors in a timely manner, resulting in lost sales;
- misappropriation of our proprietary information, including our trade secrets and know-how;
- termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us; and
- reliance on the third party for regulatory compliance, quality assurance and safety and pharmacovigilance reporting.

The FDA and other comparable non-U.S. regulatory authorities require manufacturers to register manufacturing facilities. The FDA and other comparable non-U.S. regulatory authorities also inspect these facilities to confirm compliance with cGMP. Contract manufacturers may face manufacturing or quality control problems causing drug substance production and shipment delays or a situation where the contractor may not be able to maintain compliance with the applicable cGMP requirements. We may have little to no control regarding the occurrence of third-party manufacturer incidents. Failure by our third-party manufacturers and suppliers to pass such inspections and otherwise satisfactorily complete the FDA approval regimen with respect to our product candidate may result in regulatory actions such as the issuance of FDA Form 483 notices of observations, warning letters or injunctions or the loss of operating licenses. In addition, our third-party manufacturers and suppliers are subject to numerous environmental, health and safety laws and regulations, including those governing the handling, use, storage, treatment and disposal of waste products, and failure to comply with such laws and regulations could result in significant costs associated with civil or criminal fines and penalties for such third parties. Any failure to comply with cGMP requirements or other FDA or comparable non-U.S. regulatory requirements could negatively impact our clinical research activities and our ability to develop OPT-302 or any future product candidates and market our products following approval.

If OPT-302 or any future product candidates are approved by the FDA or other comparable non-U.S. regulatory authorities for commercial sale, we may need to manufacture such product candidate in larger quantities. We intend to use third-party manufacturers for commercial quantities of OPT-302 to the extent we

advance this product candidate and other product candidates. Our manufacturers may not be able to successfully increase the manufacturing capacity for any of our product candidates in a timely or efficient manner, or at all. If we are unable to successfully increase the manufacturing capacity for a product candidate, the regulatory approval or commercial launch of that product candidate may be delayed or there may be a shortage in the supply of the product candidate.

In addition, the operations of our third-party manufacturers may be subject to earthquakes, power shortages, telecommunications failures, failures or breaches of information technology systems, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics, such as the recent COVID-19 pandemic, and other natural or man-made disasters or business interruptions. Damage or extended periods of interruption to our facilities due to fire, natural disaster, power loss, communications failure, unauthorized entry or other events could cause us to cease or delay development of some or all of our product candidates. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption.

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

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

The manufacture of biologic products is complex and we are subject to many manufacturing risks, any of which could substantially increase our costs and limit supply of our products.

The manufacture of biologic products is complex and requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of biologic products often encounter difficulties in production, particularly in scaling up and validating initial production and ensuring the avoidance of contamination. These problems include difficulties with production costs and yields, quality control, including stability of the product, quality assurance testing, operator error and shortages of qualified personnel, as well as compliance with strictly enforced federal, state and non-U.S. regulations. We cannot assure you that any stability or other issues relating to the manufacture of OPT-302 will not occur in the future.

The process of manufacturing OPT-302 is complex, highly regulated and subject to several risks, including:

- the process of manufacturing biologics is susceptible to product loss due to contamination, equipment failure, improper installation or operation of equipment, vendor or operator error and improper storage conditions. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects and other supply disruptions. If microbial, viral or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, the manufacturing facilities may need to be closed for an extended period of time to investigate and eliminate the contamination;

- the manufacturing facilities in which our products are made could be negatively affected by equipment failures, labor and raw material shortages, financial difficulties of our contract manufacturers, natural disasters, power failures, local political unrest and numerous other factors; and

- any adverse developments affecting manufacturing operations for our product candidates may result in shipment delays, inventory shortages, lot failures, and for any approved products, product withdrawals, or recalls or other interruptions in the supply of our products. We may also have to record inventory

write-offs and incur other charges and expenses for products that fail to meet specifications, undertake costly remediation efforts or seek costlier manufacturing alternatives.

To date, OPT-302 has been manufactured by a single third-party manufacturer, Patheon, solely for preclinical studies and Phase 1, 2 and 3 trials Any such failure will require us to seek alternative manufacturing sources, which may result in considerable additional expense and delays in our planned clinical trials. We have limited process development capabilities and have access only to external manufacturing capabilities. We do not have and we do not currently plan to acquire or develop the facilities or capabilities to manufacture bulk drug substance or filled drug product for use in human clinical trials or commercialization. Any delay or interruption in the supply of clinical trial materials, including as a result of breach by us or Patheon of our agreement with Patheon, or our inability to agree to the terms of supply or related services in any statement of work, could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

Changes in methods of product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates proceed through nonclinical studies to late-stage clinical trials towards potential approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause OPT-302 or any future product candidate to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the altered materials. Such changes may also require additional testing, FDA notification or FDA approval. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of OPT-302 or any future product candidate or jeopardize our ability to commence sales and generate revenue.

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

We currently rely on, and expect to continue to rely on, third parties, such as CROs, clinical data management organizations, medical institutions, consultants and clinical investigators, to conduct our clinical trials and certain aspects of our research and development activities. 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 and such alternative arrangements may not be available on terms acceptable to us.

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. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and clinical trial protocols. Moreover, the FDA requires us to comply with standards, commonly referred to as current Good Clinical Practices, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We are also required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements, standard operating procedures or clinical trial protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for OPT-302 or any future product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development, marketing approval and/or commercialization of OPT-302 or any future product candidates, producing additional losses and depriving us of potential revenue.

Disputes under key agreements or conflicts of interest with our scientific advisors or clinical investigators could delay or prevent development or commercialization of our product candidates.

Any agreements we have or may enter into with third parties, such as collaboration, license, formulation supplier, manufacturing, clinical research organization or clinical trial agreements, may give rise to disputes regarding the rights and obligations of the parties. Disagreements could develop over contract interpretation, rights to ownership or use of intellectual property, the scope and direction of research and development, the approach for regulatory approvals or commercialization strategy. We intend to conduct research programs in a range of therapeutic areas, but our pursuit of these opportunities could result in conflicts with the other parties to these agreements that may be developing or selling pharmaceuticals or conducting other activities in these same therapeutic areas. Any disputes or commercial conflicts could lead to the termination of our agreements, delay progress of our product development programs, compromise our ability to renew agreements or obtain future agreements, lead to the loss of intellectual property rights, result in increased financial obligations for us or result in costly litigation.

We work with outside scientific advisors and collaborators at academic and other institutions that assist us in our research and development efforts. Our scientific advisors are not our employees and may have other commitments that limit their availability to us. If a conflict of interest between their work for us and their work for another entity arises, we may lose their services.

We may seek to establish commercial collaborations for our product candidates, and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. We may decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of our product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator’s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator’s evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or comparable non-U.S. regulatory authorities, the potential market for the product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products and the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborators may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms, or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Risks Related to Employee Matters and Managing Our Growth

We must attract and retain highly skilled employees in order to succeed. If we are not able to retain our current senior management team and our scientific advisors or continue to attract and retain qualified scientific, technical and business personnel, our business will suffer.

We may not be able to attract or retain qualified personnel and consultants due to the intense competition for such individuals in the biotechnology and pharmaceutical industries. In particular, we are in the process of hiring employees, including senior employees, in the United States as we continue clinical development of OPT-302 and prepare for potential commercialization. The hiring environment in the United States for such candidates is extremely competitive. Many of the other pharmaceutical companies that we compete against for qualified personnel have greater financial and other resources, different risk profiles and a longer history in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high-quality candidates than what we have to offer. If we are not able to attract and retain necessary personnel and consultants to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development and commercial objectives, our ability to raise additional capital and our ability to implement our business strategy.

Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the development, regulatory, commercialization and business development expertise of the members of our executive team, as well as other key employees and consultants. If we lose one or more of our executive officers or other key employees or consultants, our ability to implement our business strategy successfully could be seriously harmed. Any of our executive officers or other key employees or consultants may terminate their employment at any time with three months' notice, subject to certain exceptions, and replacing such individuals may be difficult and time-consuming because of the limited number of individuals in our industry with the necessary breadth of skills and experience. Competition to hire and retain employees and consultants from this limited pool is intense, and we may be unable to hire, train, retain or motivate such individuals. Additionally, we do not currently maintain "key person" life insurance on the lives of our executives or any of our employees. This lack of insurance means that we may not receive adequate compensation for the loss of the services of these individuals. If we are unable to continue to attract and retain high-quality personnel, the rate and success with which we can discover and develop product candidates and our business will be limited.

Our employees, contractors, vendors, principal investigators, consultants and future partners may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, contractors, vendors, principal investigators, consultants or future partners. Misconduct by these parties could include failures to comply with FDA or comparable non-U.S. authority regulations, to provide accurate information to the FDA or comparable non-U.S. regulators, to comply with U.S. federal and state and non-U.S. healthcare fraud and abuse laws and regulations, to report financial information or data timely, completely or accurately, or to 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. Third-party misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. Although we have adopted a Code of Conduct, it is not always possible to identify and deter 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 resulting from this misconduct and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions. If we or our future partners market products in a manner that violates fraud and abuse and other healthcare laws, or if we or our future partners violate government price reporting laws, we or our future partners may be subject to administrative civil and/or criminal penalties, among other sanctions.

Most states also have statutes or regulations similar to these federal laws, which may apply to items such as pharmaceutical products and services reimbursed by private insurers. We and/or our future partners may be subject to administrative, civil and criminal sanctions for violations of any of these federal and state laws. Pharmaceutical

and other healthcare companies have been prosecuted under these laws for a variety of promotional and marketing activities, such as: providing free trips, free goods, sham consulting fees and grants and other monetary benefits to prescribers; reporting to pricing services inflated average wholesale prices that were then used by federal programs to set reimbursement rates; engaging in off-label promotion; and submitting inflated best price information to the Medicaid Rebate Program to reduce liability for Medicaid rebates. Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations.

We may encounter difficulties in managing our growth, which could negatively impact our operations.

As we advance our clinical development programs for product candidates, seek regulatory approval in the United States and elsewhere and increase the number of ongoing product development programs, we anticipate that we will need to increase our product development, scientific and administrative headcount. In particular, as we progress our Phase 3 clinical trials for OPT-302 in combination with anti-VEGF-A therapy for the treatment of wet AMD, we will require additional key staff for clinical development operations as well as additional key financial and administrative personnel. We will also need to establish commercial capabilities in order to commercialize any product candidates that may be approved. Such an evolution may impact our strategic focus and our deployment and allocation of resources.

Our ability to manage our operations and growth effectively depends upon the continual improvement of our procedures, reporting systems and operational, financial and management controls. We currently have no experience as a company in or infrastructure for sales, marketing and distribution, and our operations are currently limited to clinical development activities and as our operations expand, we likely will need to manage additional relationships with such third parties. We may not be able to implement administrative and operational improvements in an efficient or timely manner and may discover deficiencies in existing systems and controls. If we do not meet these challenges, we may be unable to execute our business strategies and may be forced to expend more resources than anticipated addressing these issues.

We may acquire additional technology and complementary businesses in the future. Acquisitions involve many risks, any of which could materially harm our business, including the diversion of management’s attention from core business concerns, failure to effectively exploit acquired technologies, failure to successfully integrate the acquired business or realize expected synergies or the loss of key employees from either our business or the acquired businesses.

If OPT-302 or any future product candidate is approved, we intend either to establish a sales and organization with technical expertise and supporting distribution capabilities to commercialize OPT-302 or any future product candidate or to outsource such functions to one or more third parties. Either of these options would be expensive and time-consuming. Some or all of these costs may be incurred in advance of any approval of OPT-302 or any future product candidate. In addition, we may not be able to hire a sales force that is sufficient in size or has adequate expertise in the medical markets that we intend to target.

If we are unable to successfully manage our growth and the increased complexity of our operations, our business, financial position, results of operations and prospects may be harmed.

Risks Related to Intellectual Property

Our success depends upon our ability to obtain and maintain intellectual property protection for our products and technologies.

Our success will depend in significant part on our current or future licensors’, licensees’ or collaborators’ ability to establish and maintain adequate protection of our owned and licensed intellectual property covering the product candidates we plan to develop, and the ability to develop these product candidates and commercialize the products resulting therefrom, without infringing the intellectual property rights of others. In addition to taking other steps to protect our intellectual property, we hold issued patents, we have applied for patents, and we intend to continue to apply for, patents with claims covering our technologies, processes and product candidates when and where we deem it appropriate to do so. We have filed patent applications both in the United States and in certain non-U.S. jurisdictions to obtain patent rights to inventions we have developed, with claims directed to compositions of matter, methods of use and other technologies relating to our programs. There can be no assurance

that any of these patent applications will issue as patents or, for those applications that do mature into patents, that the claims of the patents will exclude others from making, using or selling our product candidates or products that compete with or are similar to our product candidates. In countries where we have not sought and do not seek patent protection, third parties may be able to manufacture and sell our product candidates without our permission, and we may not be able to stop them from doing so.

With respect to patent rights, we do not know whether any of the pending patent applications for any of our product candidates will result in the issuance of patents that effectively protect our technologies, processes and product candidates, or if any of our issued patents or our current or future licensors', licensees' or collaborators' issued patents will effectively prevent others from commercializing competitive technologies, processes and products. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or in some cases not at all, until they are issued as a patent. Therefore, we cannot be certain that we or our current or future licensors, licensees or collaborators were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we or our current or future licensors, licensees or collaborators were the first to file for patent protection of such inventions. For a description of our patent portfolio, see "Item 4B Business Overview" of this annual report.

Any changes we make to OPT-302 or any future product candidates to cause them to have what we view as more advantageous properties may not be covered by our existing patents and patent applications, and we may be required to file new applications and/or seek other forms of protection for any such altered product candidates. The patent landscape surrounding the technology underlying our product candidates is potentially crowded, and there can be no assurance that we would be able to secure patent protection that would adequately cover an alternative to OPT-302 or any future product candidates.

The patent prosecution process is expensive and time-consuming, and we and our current or future licensors, licensees or collaborators may not be able to prepare, file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we or our current or future licensors, licensees or collaborators will fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection for them. Moreover, in some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain or enforce the patents, covering technology that we license from or license to third parties and may be reliant on our current or future licensors, licensees or collaborators to perform these activities, which means that these patent applications may not be prosecuted, and these patents enforced, in a manner consistent with the best interests of our business. If our current or future licensors, licensees or collaborators fail to establish, maintain, protect or enforce such patents and other intellectual property rights, such rights may be reduced or eliminated. If our current or future licensors, licensees or collaborators are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised.

Similar to the patent rights of other biotechnology companies, the scope, validity and enforceability of our owned and licensed patent rights generally are highly uncertain and involve complex legal and factual questions. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. In recent years, these areas have been the subject of much litigation in the industry. As a result, the issuance, scope, validity, enforceability and commercial value of our and our current or future licensors', licensees' or collaborators' patent rights are highly uncertain. Our and our current or future licensors', licensees' or collaborators' pending and future patent applications may not result in patents being issued that protect our technology or product candidates, or products resulting therefrom, in whole or in part, or that effectively prevent others from commercializing competitive technologies and products. The patent examination process may require us or our current or future licensors, licensees or collaborators to narrow the scope of the claims of pending and future patent applications, which would limit the scope of patent protection that is obtained, if any. Our and our current or future licensors', licensees' or collaborators' patent applications cannot be enforced against third parties practicing the technology that is currently claimed in such applications unless and until a patent issues from such applications, and then only to the extent the claims that issue are broad enough to cover the technology being practiced by those third parties.

Furthermore, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after the resulting products are commercialized. As a result, our owned and in-licensed patents may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. We expect to seek extensions of patent terms for our issued patents, where available. This includes in the United States under the Hatch-Waxman Act,

which permits a patent term extension of up to five years beyond the original expiration date of the patent as compensation for regulatory delays. However, such a patent term extension cannot lengthen the remaining term of a patent beyond a total of 14 years from the product's approval date. Only one patent applicable to each regulatory review period may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended, with extended rights limited to the approved product, its approved uses and/or its manufacture. During the period of patent term extension, the claims of a patent are not enforceable for their full scope, but are instead limited to the scope of the approved product. In addition, the applicable authorities, including the FDA in the United States, and any comparable non-U.S. regulatory authorities, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. In addition, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to the expiration of relevant patents or otherwise failing to satisfy applicable requirements. If this occurs, any period during which we have the right to exclusively market our product will be shorter than we would otherwise expect, and our competitors may obtain approval of and launch products earlier than might otherwise be the case.

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

The legal protection afforded to inventors and owners of intellectual property in countries outside of the United States may not be as protective or effective as that in the United States and we may, therefore, be unable to acquire and enforce intellectual property rights outside the United States to the same extent as in the United States. Whether filed in the United States or abroad, our patent applications may be challenged or may fail to result in issued patents.

In addition, our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from practicing our technologies or from developing or commercializing competing products. Furthermore, others may independently develop or commercialize similar or alternative technologies or drugs, or design around our patents. Our patents may be challenged, invalidated, circumvented or narrowed, or fail to provide us with any competitive advantages. In many non-U.S. countries, patent applications and/or issued patents, or parts thereof, must be translated into the native language. If our patent applications or issued patents are translated incorrectly, they may not adequately cover our technologies; in some countries, it may not be possible to rectify an incorrect translation, which may result in patent protection that does not adequately cover our technologies in those countries.

Filing, prosecuting, enforcing and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States may be less extensive than those in the United States. In addition, the laws of some non-U.S. countries do not protect intellectual property rights to the same extent as federal and certain state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with OPT-302 or any future product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in non-U.S. jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals. This could make it difficult for us to stop the infringement of our patents or the marketing of competing products in violation of our proprietary rights, generally. Proceedings to enforce our patent rights in non-U.S. jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could place our patent applications at risk of not issuing and could provoke third parties to assert claims against us or our collaborator. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful.

The requirements for patentability differ and certain countries have heightened requirements for patentability, requiring more disclosure in the patent application. In addition, certain countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In those countries, we may have limited remedies if patents are infringed or if we are compelled to grant a license to a third party, which could

materially diminish the value of those patents. This could limit our potential revenue opportunities. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. Accordingly, our efforts to enforce intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license.

Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect OPT-302 and any future product candidates.

As is the case with other biotechnology and pharmaceutical companies, our success is heavily dependent on intellectual property rights, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves technological and legal complexity, and obtaining and enforcing biopharmaceutical patents is costly, time-consuming and inherently uncertain. The U.S. Supreme Court in recent years has issued rulings either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations or ruling that certain subject matter is not eligible for patent protection. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by Congress, the federal courts, the USPTO and equivalent bodies in non-U.S. jurisdictions, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce existing patents and patents we may obtain in the future.

Patent reform laws, such as the Leahy-Smith America Invents Act, or the Leahy-Smith Act, as well as changes in how patent laws are interpreted, could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. The Leahy-Smith Act made a number of significant changes to U.S. patent law. These include provisions that affect the filing and prosecution strategies associated with patent applications, including a change from a “first-to-invent” to a “first-inventor-to-file” patent system, and a change allowing third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO-administered post-grant proceedings, including post-grant review, *inter partes* review and derivation proceedings. The USPTO has developed regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act and, in particular, the “first-inventor-to-file” provisions, became effective in 2013. The Leahy-Smith Act and its implementation may increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could harm our business, financial condition and results of operations.

We may be unable to obtain intellectual property rights or technology necessary to develop and commercialize OPT-302 and any future product candidates.

The patent landscape around our programs is complex, and there may be one or more third-party patents and patent applications containing subject matter that might be relevant to OPT-302. Depending on what claims may ultimately issue from these patent applications, and how courts construe the issued patent claims, as well as depending on the ultimate formulation and method of use of OPT-302 or any future product candidates, we may need to obtain a license to practice the technology claimed in such patents. There can be no assurance that such licenses will be available on commercially reasonable terms, or at all. If a third party does not offer us a necessary license or offers a license only on terms that are unattractive or unacceptable to us, we might be unable to develop and commercialize one or more of our product candidates, which would harm our business, financial condition and results of operations. Moreover, even if we obtain licenses to such intellectual property, but subsequently fail to meet our obligations under the relevant license agreements, or such license agreements are terminated for any other reasons, we may lose our rights to the technologies licensed under those agreements.

The licensing or acquisition of third-party intellectual property rights is an area in which many companies operate that have interests that are in conflict with ours, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment, or at all. If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant

program or product candidate, which could harm our business, financial condition, results of operations and prospects.

We may become involved in lawsuits or other proceedings to protect or enforce our intellectual property, which could be expensive, time-consuming and unsuccessful and have a negative effect on the success of our business.

Third parties may infringe our patents or misappropriate or otherwise violate our intellectual property rights. In the future, we may initiate legal proceedings to enforce or defend our intellectual property rights, to protect our trade secrets or to determine the validity or scope of intellectual property rights we own or control. Also, third parties may initiate legal proceedings against us to challenge the validity or scope of intellectual property rights we own, control or to which we have rights. For example, generic or biosimilar drug manufacturers or other competitors or third parties may challenge the scope, validity or enforceability of our patents, requiring us to engage in complex, lengthy and costly litigation or other proceedings. These proceedings can be expensive and time-consuming and many of our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon or misappropriating intellectual property rights we own, control or have rights to, particularly in countries where the laws may not protect those rights as fully as in the United States. Litigation could result in substantial costs and diversion of management resources, which could harm our business and financial results. In addition, if we initiated legal proceedings against a third party to enforce a patent covering a product candidate, the defendant could counterclaim that such patent is invalid or unenforceable. In patent litigation in the United States, defendants usually assert counterclaims alleging invalidity or unenforceability. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. In an infringement or declaratory judgment proceeding, a court may decide that a patent owned by or licensed to us is invalid or unenforceable, or may refuse to stop the other party from using the subject matter alleged to be infringing on the grounds that our patents do not cover that subject matter. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, narrowed, held unenforceable or interpreted in such a manner that would not preclude third parties from entering the market with competing products.

Third-party pre-issuance submission of prior art to the USPTO, or opposition, derivation, revocation, reexamination, *inter partes* review or interference proceedings, or other pre-issuance or post-grant proceedings or other patent office proceedings or litigation in the United States or other jurisdictions provoked by third parties or brought by us, may be necessary to determine the inventorship, priority, patentability or validity of inventions with respect to our patents or patent applications. An unfavorable outcome could leave our technology or product candidates without patent protection, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or could require us to obtain license rights from the prevailing party in order to be able to manufacture or commercialize our product candidates without infringing third-party patent rights. Our business could be harmed if the prevailing party in such a case does not offer us a license on commercially reasonable terms, or at all. Even if we obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Even if we successfully defend such litigation or proceeding, we may incur substantial costs and our defense may distract our management and other employees.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. In addition, many non-U.S. jurisdictions have rules of discovery that are different than those in the United States and that may make defending or enforcing our patents extremely difficult. 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 negatively affect the price of the ADSs and our ordinary shares.

Third parties may initiate legal proceedings against us alleging that we infringe their intellectual property rights, the outcome of which would be uncertain and could harm our business.

Our commercial success depends upon our ability to develop, manufacture, market and sell OPT-302 and any future product candidates that we may develop and use our proprietary technologies without infringing, misappropriating or otherwise violating the intellectual property and proprietary rights of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. Third parties may initiate legal proceedings against us alleging that we infringe their intellectual property rights or we may initiate legal proceedings against third parties to challenge the validity or scope of intellectual property rights controlled by third parties, including in oppositions, interferences, revocations, reexaminations, *inter partes* review or derivation proceedings before the USPTO or its counterparts in other jurisdictions. These proceedings can be expensive and time-consuming and many of our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can.

We could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent of a third party. A finding of infringement could prevent us from commercializing OPT-302 or any future product candidates or force us to cease some of our business operations, which could materially harm our business.

We may not be aware of all third-party intellectual property rights potentially relating to OPT-302 or any future product candidates and technologies. We are not aware of any facts that would lead us to conclude that the valid and enforceable claims of any third-party patents would reasonably be interpreted to cover our product candidates. As to pending third-party applications, we cannot predict with any certainty which claims will issue, if any, or the scope of such issued claims. Even if we believe third-party intellectual property claims are without merit, there is no assurance that a court would find in our favor on questions of infringement, validity, enforceability or priority. A court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could materially and negatively affect our ability to commercialize any product candidates we may develop and any other product candidates or technologies covered by the asserted third-party patents. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If any such third-party patents (including those that may issue from such applications) were successfully asserted against us or other commercialization partners and we were unable to successfully challenge the validity or enforceability of any such asserted patents, then we and other commercialization partners may be prevented from commercializing our product candidates, or may be required to pay significant damages, including treble damages and attorneys' fees if we are found to willfully infringe the asserted patents, or obtain a license to such patents, which may not be available on commercially reasonable terms, or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. Any of the foregoing would harm our business, financial condition and operating results.

Although we have reviewed certain third-party patents and patent filings that we believe may be relevant to our therapeutic candidates or products, we have not conducted a freedom-to-operate search or analysis for any of our therapeutic candidates or products, and we may not be aware of patents or pending or future patent applications that, if issued, would block us from commercializing our therapeutic candidates or products. Thus, we cannot guarantee that our therapeutic candidates or products, or our commercialization thereof, do not and will not infringe any third party's intellectual property.

We may be subject to claims by third parties asserting misappropriation of intellectual property, or claiming ownership of what we regard as our own intellectual property.

Although we seek to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed confidential information or intellectual property, including trade secrets or other proprietary information, of any such employee's former employer, or that third parties have an interest in our patents as an inventor or co-inventor. Litigation may be necessary to defend against these claims. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or the services of personnel or sustain other damages. Such intellectual property rights could be awarded to a third party, and we

could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms, or at all. Even if we successfully prosecute or defend against such claims, litigation could result in substantial costs and distract management.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could harm our business, financial condition, results of operations and prospects.

Our inability to protect our confidential information and trade secrets would harm our business and competitive position.

In addition to seeking patents for some of our technology and product candidates, we also rely substantially on trade secrets, including unpatented know-how, technology and other proprietary materials and information, to maintain our competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. However, these steps may be inadequate, we may fail to enter into agreements with all such parties or any of these parties may breach the agreements and disclose our trade secrets and there may be no adequate remedy available for such breach of an agreement. We cannot assure you that our trade secrets will not be disclosed or that we can meaningfully protect our trade secrets. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time consuming, and the outcome is unpredictable. In addition, some courts both within and outside the United States may be less willing, or unwilling, to protect trade secrets. If a competitor lawfully obtained or independently developed any technology or information that we protect as trade secret, we would have no right to prevent such competitor from using that technology or information to compete with us, which could harm our competitive position.

Intellectual property rights do not necessarily address all potential threats.

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

- others may be able to make products that are similar to OPT-302 and any future product candidates we may develop or utilize similar technology but that are not covered by the claims of the patents that we exclusively license or may own in the future;
- we, our licensors or our future collaborators, might not have been the first to make the inventions covered by the issued patents and pending patent applications that we exclusively license or may own in the future;
- we, our licensors or our future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or exclusively licensed intellectual property rights;
- it is possible that our pending patent applications or those that we may file in the future, including those that we have licensed, will not result in issued patents;
- issued patents to which we hold rights may be held invalid or unenforceable, including as a result of legal challenges by our competitors;

- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in major commercial markets in which we do not have sufficient patent rights to stop such sales;

- we may not develop additional proprietary technologies that are patentable;

- the patents of others may be asserted against our product candidates and technologies in a manner that harms our business; and

- we may choose not to file a patent application in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such trade secrets or know-how.

Should any of these events occur, they could harm our business, financial condition, results of operations and prospects.

If our trademarks and trade names are not maintained and adequately protected, we may not be able to build name recognition in our markets of interest, and our business may be negatively affected.

Failure to obtain trademark registrations in the future, could limit our ability to protect and enforce our trademarks and impede our marketing efforts in the countries in which we operate. We may not be able to protect our rights to trademarks and trade names which we may need to build name recognition with potential partners or customers in our markets of interest. As a means to enforce any future trademark rights and prevent infringement, we may be required to file trademark claims against third parties or initiate trademark opposition proceedings. This can be expensive and time consuming and can strain the financial resources of a company of our size, and we may not be successful in enforcing our trademark rights. In addition, our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented, declared generic or determined to be infringing on other marks.

Future trademark applications in the United States and in other non-U.S. jurisdictions where we may file may not be allowed or may subsequently be opposed. Even if these applications result in registration of trademarks, third parties may challenge our use or registration of these trademarks in the future. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be negatively affected.

Our product candidates may face competition sooner than anticipated from biosimilar products.

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

There is a risk that any exclusivity we may be afforded if any of our product candidates are approved as a biologic product under a BLA could be shortened due to congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for generic or biosimilar competition sooner than anticipated. Moreover, the extent to which a biosimilar product, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biologic products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing. In addition, a competitor could decide to forego the biosimilar approval path and submit a full BLA after completing its own preclinical studies and clinical trials. In such cases, any exclusivity to which we may be eligible under the BPCIA would not prevent the competitor from marketing its product as soon as it is approved.

In Europe, the European Commission has granted marketing authorizations for several biosimilar products pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data supporting approval of an innovative biological product, but will not be able to market it until 10 years after the time of approval of the innovative product. This 10-year marketing exclusivity period may be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilar products in other countries that could compete with our products, if approved.

If competitors are able to obtain marketing approval for biosimilars referencing our product candidates, if approved, such products may become subject to competition from such biosimilars, with the attendant competitive pressure and potential adverse consequences. Such competitive products may be able to immediately compete with us in each indication for which our product candidates may have received approval.

Risks Related to Ownership of the ADSs

An active and liquid market for our securities may fail to develop, which could harm the market price of the ADSs.

Although our ADSs are listed in the United States on Nasdaq, an active trading market for the ADSs may never develop, or if developed, this market may not be sustained. We cannot predict the effect of this dual listing on the value of the ordinary shares and ADSs. However, the dual listing of the ordinary shares and ADSs may dilute the liquidity of these securities in one or both markets and may adversely affect the development of an active trading market for the ADSs.

The trading price and volume of the ADSs may be volatile, and ADSs holders could incur substantial losses.

The price and trading volumes of our ordinary shares and ADSs may be significantly affected by events such as announcements regarding scientific and clinical results concerning product candidates currently being developed by us, our collaboration partners or our main competitors, changes in market conditions related to our sector of activity, announcements of new contracts, technological innovations and collaborations by us or our main competitors, developments concerning intellectual property rights, as well as the development, regulatory approval and commercialization of new products by us or our main competitors and changes in our financial results.

In addition, equity markets may be subject to considerable price and trading volume fluctuations, and often, these movements do not reflect the operational and financial performance of the listed companies concerned. In particular, biotechnology companies' share prices have been highly volatile in the past and may continue to be highly volatile in the future. As we operate in a single industry, we are especially vulnerable to these factors to the extent that they affect our industry. Fluctuations in the stock market as well as the macroeconomic environment could significantly affect the price of the ADSs. As a result of this volatility, investors may not be able to sell their ADSs at or above the price originally paid for the security. The market price and trading volume for the ADSs may be influenced by many factors, including:

- actual or anticipated fluctuations in our financial condition and operating results;
- actual or anticipated changes in our growth rate relative to our competitors;
- competition from existing products or new products that may emerge;
- announcements by us or our competitors of significant acquisitions, divestitures, spin-offs, strategic partnerships, joint ventures, collaborations, capital commitments or changes in business strategy;
- adverse results of delays in our or any of our competitors' preclinical studies or clinical trials;
- adverse regulatory decisions, including failure to receive regulatory approval for any of our product candidates;
- the termination of a strategic alliance or the inability to establish additional strategic alliances;

- failure to meet or exceed financial estimates and projections of the investment community or that we provide to the public;
- issuance of new or updated research or reports by securities analysts;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- ADS price and volume fluctuations attributable to inconsistent trading volume levels of the ADSs;
- price and volume fluctuations in trading of our ordinary shares on the ASX;
- short selling or other market manipulation activities;
- fluctuations of exchange rates between the U.S. dollar and the Australian dollar;
- additions or departures of key management or scientific personnel;
- disruptions in our supply or manufacturing arrangements;
- disputes or other developments related to proprietary rights, including patents, litigation matters and our ability to obtain patent and other intellectual property protection for our technologies;
- changes to coverage policies or reimbursement levels by commercial third-party payors and government payors and any announcements relating to coverage policies or reimbursement levels;
- litigation involving our company;
- announcement or expectation of additional debt or equity financing efforts;
- natural disasters or other calamities or disease outbreaks, such as the COVID-19 pandemic;
- sales of the ADSs by us, our affiliates or our other shareholders; and
- general economic and market conditions.

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

We do not currently intend to pay dividends on our securities and, consequently, your ability to achieve a return on your investment will depend on appreciation in the price of the ADSs.

We have not declared or paid any cash dividends on our ordinary shares since February 2005 and do not currently intend to do so for the foreseeable future. We currently intend to invest our future earnings, if any, to fund our operations and growth. Therefore, you are not likely to receive any dividends on your ADSs for the foreseeable future and the success of an investment in the ADSs will depend upon any future appreciation in its value. Consequently, investors may need to sell all or part of their holdings of the ADSs after price appreciation, which may never occur, as the only way to realize any future gains on their investment. There is no guarantee that the ADSs will appreciate in value or even maintain the price at which our shareholders have purchased them. Investors seeking cash dividends should consider not purchasing the ADSs.

While we do not anticipate paying any cash dividends on our ordinary shares in the foreseeable future, if such a dividend is declared, 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. 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 take any other action to permit the distribution of 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 negatively impact the value of your ADSs. In addition, exchange rate fluctuations may affect the amount of Australian dollars that we are able to distribute, and the amount in U.S. dollars that our shareholders receive upon the payment of cash dividends or other distributions we declare and pay in Australian dollars, if any. These factors could harm the value of the ADSs, and, in turn, the U.S. dollar proceeds that holders receive from the sale of the ADSs.

Future sales of ordinary shares or ADSs by existing holders could depress the market price of the ordinary shares or ADSs.

We had a total of 351,003,541 ordinary shares outstanding as of June 30, 2021, including the 7,493,568 ordinary shares underlying ADSs that were issued upon the exercise of pre-funded warrants in March and June 2021. As of the date of this annual report, the exercise of all outstanding options exercisable for ordinary shares would enable the subscription of new ordinary shares representing approximately 3.25% of the diluted share capital. The ordinary shares subject to subscription under outstanding options exercisable for ordinary shares will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations. Sales of a large number of the ordinary shares in the public market could depress the market price of the ADSs. If these additional ordinary shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of the ordinary shares and ADSs could decline substantially, which could impair our ability to raise additional capital through the issuance of ordinary shares, ADSs or other securities in the future.

The dual listing of our ordinary shares and the ADSs may negatively impact the liquidity and value of the ADSs.

Our ADSs are listed on Nasdaq and our ordinary shares are listed on the ASX. We cannot predict the effect of this dual listing on the value of our ordinary shares and ADSs. However, the dual listing of our ordinary shares and ADSs may dilute the liquidity of these securities in one or both markets and may negatively impact the development of an active trading market for the ADSs in the United States. The price of the ADSs could also be negatively impacted by trading in our ordinary shares on the ASX.

We will incur significant increased costs as a result of operating as a company with ADSs that are publicly traded in the United States, and our management will be required to devote substantial time to new compliance initiatives.

As a company whose ADSs are publicly traded in the United States, we have incurred and will continue to incur significant legal, accounting, insurance and other expenses. In addition, the Sarbanes-Oxley Act, Dodd-Frank Wall Street Reform and Consumer Protection Act and related rules implemented by the United States Securities and Exchange Commission, or SEC, and Nasdaq have imposed various requirements on public companies listed in the United States including requiring establishment and maintenance of effective disclosure and financial controls. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives, and we will need to add additional personnel and build our internal compliance infrastructure. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. These laws and regulations could also make it more difficult and expensive for us to attract and retain qualified persons to serve on our board of directors, our board committees or as our senior management. Furthermore, if we are unable to satisfy our obligations as a public company listed in the United States, we could be subject to delisting of the ADSs, fines, sanctions and other regulatory action and potentially civil litigation.

U.S. investors may have difficulty enforcing civil liabilities against our company, our directors or members of senior management and the experts named in this annual report.

Certain members of our senior management and board of directors named in this annual report are non-residents of the United States, and a substantial portion of the assets of such persons are located outside the United States. As a result, it may be impracticable to serve process on such persons in the United States or to enforce judgments obtained in U.S. courts against them based on civil liability provisions of the securities laws of the United States. Even if you are successful in bringing such an action, there is doubt as to whether Australian courts would enforce certain civil liabilities under U.S. securities laws in original actions or judgments of U.S. courts based upon these civil liability provisions. In addition, awards of punitive damages in actions brought in the United States or elsewhere may be unenforceable in Australia or elsewhere outside the United States. An award for monetary damages under U.S. securities laws would be considered punitive if it does not seek to compensate the

claimant for loss or damage suffered and is intended to punish the defendant. The enforceability of any judgment in Australia will depend on the particular facts of the case as well as the laws and treaties in effect at the time. The United States and Australia do not currently have a treaty or statute providing for recognition and enforcement of the judgments of the other country (other than arbitration awards) in civil and commercial matters.

As a result, our public shareholders may have more difficulty in protecting their interests through actions against us, our management or our directors than would shareholders of a corporation incorporated in a jurisdiction in the United States. In addition, as a company incorporated in Australia, the provisions of the Corporations Act 2001 (Cth), or the Corporations Act, regulate the circumstances in which shareholder derivative actions may be commenced which may be different, and in many ways less permissive, than for companies incorporated in the United States.

Australian takeover laws may discourage takeover offers being made for us or may discourage the acquisition of a significant position in our ordinary shares or ADSs.

We are incorporated in Australia and are subject to the takeover laws of Australia. Among other things, we are subject to the Corporations Act. Subject to a range of exceptions, the Corporations Act prohibits the acquisition of a direct or indirect interest in our issued voting shares if the acquisition of that interest will lead to a person's voting power in us increasing to more than 20%, or increasing from a starting point that is above 20% and below 90%. Australian takeover laws may discourage takeover offers being made for us or may discourage the acquisition of a significant position in our ordinary shares. This may have the ancillary effect of entrenching our board of directors and may deprive or limit our shareholders' opportunity to sell their ordinary shares and may further restrict the ability of our shareholders to obtain a premium from such transactions. See Exhibit 2.3 "Description of Securities" as well as our Constitution.

Our Constitution and Australian laws and regulations applicable to us may adversely affect our ability to take actions that could be beneficial to our shareholders.

As an Australian company we are subject to different corporate requirements than a corporation organized under the laws of the United States. Our Constitution, as well as the Corporations Act, sets forth various rights and obligations that apply to us as an Australian company and which may not apply to a U.S. corporation. These requirements may operate differently than those of many U.S. companies. You should carefully review the summary of these matters set forth under Exhibit 2.3 "Description of Securities" as well as our Constitution, which is included as an exhibit to this annual report, prior to investing in our securities.

Your right as a holder of ADSs to participate in any future preferential subscription rights offering or to elect to receive dividends in ordinary shares may be limited, which may cause dilution to your holdings.

The deposit agreement provides that the depositary will not make rights available to you unless the distribution to ADS holders of both the rights and any related securities are either registered under the Securities Act or exempted from registration under the Securities Act of 1933, as amended, or the Securities Act. If we offer holders of our ordinary shares the option to receive dividends in either cash or shares, under the deposit agreement the depositary may require satisfactory assurances from us that extending the offer to holders of ADSs does not require registration of any securities under the Securities Act before making the option available to holders of ADSs. 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. Accordingly, ADS holders may be unable to participate in our rights offerings or to elect to receive dividends in shares and may experience dilution in their holdings. In addition, if the depositary is unable to sell rights that are not exercised or not distributed or if the sale is not lawful or reasonably practicable, it will allow the rights to lapse, in which case you will receive no value for these rights.

You may not be able to exercise your right to vote the ordinary shares underlying your ADSs.

Holders of ADSs may exercise voting rights with respect to the ordinary shares represented by the ADSs only in accordance with the provisions of the deposit agreement. The deposit agreement provides that, upon receipt of notice of any meeting of holders of our ordinary shares, the depositary will fix a record date for the determination of ADS holders who shall be entitled to give instructions for the exercise of voting rights. Upon timely receipt of notice from us, if we so request, the depositary shall distribute to the holders as of the record date (i) the notice of

the meeting or solicitation of consent or proxy sent by us and (ii) a statement as to the manner in which instructions may be given by the holders.

You may instruct the depositary to vote the ordinary shares underlying your ADSs. Otherwise, you will not be able to exercise your right to vote, unless you withdraw the ordinary shares underlying the ADSs you hold. However, you may not know about the meeting far enough in advance to withdraw those ordinary shares. If we ask for your instructions, the depositary, upon timely notice from us, will notify you of the upcoming vote and arrange to deliver our voting materials to you and will try to vote ordinary shares as you instruct. We cannot guarantee you that you will receive the voting materials in time to ensure that you can instruct the depositary to vote your ordinary shares or to withdraw your ordinary shares so that you can vote them yourself. If we do not ask for your instructions, you can still send voting instructions to the depository and the depository may try to carry out those instructions, but it is not required to do so.

Under our Constitution, any resolution to be considered at a meeting of the shareholders shall be decided on a show of hands unless a poll is demanded in accordance with the terms of our Constitution. A poll may be demanded before a vote is taken, or, in the case of a vote taken on a show of hands, immediately before or immediately after, the declaration of the result of the show of hands. Under voting by a show of hands, multiple “yes” votes by ADS holders will only count as one “yes” vote and will be negated by a single “no” vote, unless a poll is demanded.

You may be subject to limitations on the transfer of your ADSs and the withdrawal of the underlying ordinary shares.

Your ADSs are transferable on the books of the depositary. However, the depositary may close its books at any time or from time to time when it deems expedient in connection with the performance of its duties. The depositary may refuse to deliver, transfer or register transfers of your ADSs generally when our books or the books of the depositary are closed, or at any time if we or the depositary think it is advisable to do so because of any requirement of law, government or governmental body, or under any provision of the deposit agreement, or for any other reason subject to your right to surrender your ADSs and receive the underlying ordinary shares. Temporary delays in the surrendering of your ADSs and receipt 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 we are paying a dividend on our ordinary shares. In addition, you may not be able to surrender your ADSs and receive the underlying ordinary shares when you 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 ADSs or to the withdrawal of ordinary shares or other deposited securities. See “Item 12D —Description of American Depositary Shares.”

Holders of ADSs are not treated as holders of our ordinary shares.

Holders of ADSs are not treated as holders of our ordinary shares, unless they surrender the ADSs to receive the ordinary shares underlying their ADSs in accordance with the deposit agreement and applicable laws and regulations. The depositary is the holder of the ordinary shares underlying the ADSs. Holders of ADSs therefore do not have any rights as holders of our ordinary shares, other than the rights that they have pursuant to the deposit agreement. See “Item 12D —Description of American Depositary Shares.”

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 outcomes to the plaintiff(s) in any such action.

The deposit agreement governing the ADSs provides that holders and beneficial owners of ADSs, including those holders and owners who acquired ADSs in secondary transactions, 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 in respect of claims under federal securities laws, against us or the depositary 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. To our knowledge, the enforceability of a jury trial waiver under the federal securities laws has not been finally adjudicated by a federal court. However, we believe that a jury trial waiver provision is generally enforceable under the laws of the State of New York, which govern the deposit agreement, by a court of the State of New York or a federal court, which have non-exclusive jurisdiction over matters arising under the deposit agreement, applying such law. 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. In addition, New York courts will not enforce a jury trial waiver provision in order to bar a viable setoff or counterclaim sounding in fraud or one which is based upon a creditor's negligence in failing to liquidate collateral upon a guarantor's demand, or in the case of an intentional tort claim (as opposed to a contract dispute), none of which we believe are applicable in the case of the deposit agreement or the ADSs.

No condition, stipulation or provision of the deposit agreement or ADSs serves as a waiver by any holder or beneficial owner of ADSs or by us or the depositary of compliance with any provision of the federal securities laws. If you or any other holder or beneficial owner of ADSs brings a claim against us or the depositary in connection with such matters, you or such other holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us and/or the depositary. If a lawsuit is brought against us and/or the depositary under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may result in different outcomes than a trial by jury would have had, including results that could be less favorable to the plaintiff(s) in any such action, depending on, among other things, the nature of the claims, the judge or justice hearing such claims, and the venue of the hearing.

As the jury trial waiver relates to claims arising out of or relating to the ADSs or the deposit agreement, we believe that the waiver would likely continue to apply to ADS holders or beneficial owners who withdraw the ordinary shares from the ADS facility with respect to claims arising before the cancellation of the ADSs and the withdrawal of the ordinary shares, and the waiver would likely not apply to ADS holders or beneficial owners who subsequently withdraw the ordinary shares represented by ADSs from the ADS facility with respect to claims arising after the withdrawal. However, to our knowledge, there has been no case law on the applicability of the jury trial waiver to ADS holders or beneficial owners who withdraw the ordinary shares represented by the ADSs from the ADS facility.

We currently report our financial results under IFRS, which differs in certain significant respect from U.S. generally accepted accounting principles, or U.S. GAAP.

Currently we report our financial statements under IFRS. There have been and there may in the future be certain significant differences between IFRS and U.S. GAAP, including differences related to revenue recognition, intangible assets, share-based compensation expense, income tax and earnings per share. As a result, our financial information and reported earnings for historical or future periods could be significantly different if they were prepared in accordance with U.S. GAAP. In addition, we do not intend to provide a reconciliation between IFRS and U.S. GAAP unless it is required under applicable law. As a result, you may not be able to meaningfully compare our financial statements under IFRS with those companies that prepare financial statements under U.S. GAAP.

As a foreign private issuer, we are exempt from a number of rules under the U.S. securities laws and are permitted to file less information with the SEC than a U.S. company.

We are a foreign private issuer, as defined in the SEC's rules and regulations and, consequently, we are not subject to all of the disclosure requirements applicable to public companies organized within the United States. For example, we are exempt from certain rules under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that regulate disclosure obligations and procedural requirements related to the solicitation of proxies, consents or authorizations applicable to a security registered under the Exchange Act, including the U.S. proxy rules under Section 14 of the Exchange Act. In addition, our senior management and directors are exempt from the reporting and "short-swing" profit recovery provisions of Section 16 of the Exchange Act and related rules with respect to their purchases and sales of our securities. Moreover, while we currently make annual and semi-annual filings with respect to our listing on the ASX and expect to file financial reports on an annual and semi-annual basis, we will not be required to file periodic reports and financial statements with the SEC as frequently or as promptly as U.S. public companies and will not be required to file quarterly reports on Form 10-Q or current reports on Form 8-K under the Exchange Act. In addition, foreign private issuers are not required to file their annual report on Form 20-F until four months after the end of each fiscal year. Accordingly, there may be less publicly available information concerning our company than there would be if we were not a foreign private issuer.

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 and 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 will be subject to their corporate governance listing standards. However, Nasdaq rules permit foreign private issuers to follow the corporate governance practices of its home country. Some corporate governance practices in Australia may differ from Nasdaq corporate governance listing standards. For example, we could include non-independent directors as members of our Remuneration and Nomination committees, and our independent directors may not necessarily hold regularly scheduled meetings at which only independent members of the board of directors are present. Currently, we follow home country practice to the maximum extent possible. Therefore, our shareholders may be afforded less protection than they otherwise would have under corporate governance listing standards applicable to U.S. domestic issuers. For an overview of our corporate governance practices, see "Item 16G—Corporate Governance."

We may lose our foreign private issuer status in the future, which could result in significant additional cost and expense.

While we currently qualify as a foreign private issuer, the determination of foreign private issuer status is made annually on the last business day of an issuer's most recently completed second fiscal quarter and, accordingly, our next determination will be made on December 31, 2021. In the future, we would lose our foreign private issuer status if we to fail to meet the requirements necessary to maintain our foreign private issuer status as of the relevant determination date. For example, if 50% or more of our securities are held by U.S. residents and more than 50% of our senior management or directors are residents or citizens of the United States, we could lose our foreign private issuer status.

The regulatory and compliance costs to us under U.S. securities laws as a U.S. domestic issuer may be significantly more than costs we incur as a foreign private issuer. If we are not a foreign private issuer, we will be required to file periodic reports and registration statements on U.S. domestic issuer forms with the SEC, which are more detailed and extensive in certain respects than the forms available to a foreign private issuer. We would be required under current SEC rules to prepare our financial statements in accordance with U.S. GAAP rather than IFRS, and modify certain of our policies to comply with corporate governance practices required of U.S. domestic issuers. Such conversion of our financial statements to U.S. GAAP would involve significant time and cost. In addition, we may lose our ability to rely upon exemptions from certain corporate governance requirements on U.S. stock exchanges that are available to foreign private issuers such as the ones described above and exemptions from procedural requirements related to the solicitation of proxies.

We are an "emerging growth company" under the JOBS Act and will be able to avail ourselves of reduced disclosure requirements applicable to emerging growth companies, which could make our ordinary shares ADSs less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not "emerging growth companies," including not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We cannot predict if investors will find the ordinary shares or ADSs less attractive because we may rely on these exemptions. If some investors find the ordinary shares or ADSs less attractive as a result, there may be a less active trading market for the ordinary shares or ADSs and the price of the ordinary shares or ADSs may be more volatile. We may take advantage of these exemptions until such time that we are no longer an emerging growth company. We would cease to be an emerging growth company upon the earliest to occur of (i) the last day of the fiscal year in which we have more than US$1.07 billion in annual revenue; (ii) the last day of the fiscal year in which we qualify as a "large accelerated filer"; (iii) the date on which we have, during the previous three-year period, issued more than US$1.0 billion in non-convertible debt securities; and (iv)June 30, 2026.

As a result of being a U.S. public company, we are subject to additional regulatory compliance requirements, including Section 404, and if we fail to maintain an effective system of internal controls, we may not be able to accurately report our financial results or prevent fraud.

Pursuant to Section 404, our management will be required to assess and attest to the effectiveness of our internal control over financial reporting in connection with issuing our consolidated financial statements as of and for the fiscal year ending June 30, 2022. Section 404 also requires an attestation report on the effectiveness of internal control over financial reporting be provided by our independent registered public accounting firm beginning with our annual report following the date on which we are no longer an "emerging growth company", which may be up to five fiscal years from the initial public offering of our ADSs.

The cost of complying with Section 404 will significantly increase and management's attention may be diverted from other business concerns, which could adversely affect our results. We may need to hire more employees in the future or engage outside consultants to comply with these requirements, which will further increase expenses. If we fail to comply with the requirements of Section 404 in the required timeframe, we may be subject to sanctions or investigations by regulatory authorities, including the SEC and Nasdaq. Furthermore, if we are unable to attest to the effectiveness of our internal control over financial reporting, we could lose investor confidence in the accuracy and completeness of our financial reports, and the market price of our ordinary shares and ADSs could decline. Failure to implement or maintain effective internal control over financial reporting could also restrict our future access to the capital markets and subject each of us, our directors and our officers to both significant monetary and criminal liability. In addition, changing laws, regulations and standards relating to corporate governance and public disclosure are creating uncertainty for public companies, increasing legal and financial compliance costs and making some activities more time consuming. These laws, regulations and standards are subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expense and a diversion of management's time and attention from revenue generating activities to compliance activities. If our efforts to comply with new laws, regulations and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to their application and practice, regulatory authorities may initiate legal proceedings against us and our business, financial position, results and prospects may be adversely affected.

It is likely that we will be classified as a passive foreign investment company, which could result in adverse U.S. federal income tax consequences for U.S. holders.

In general, a non-U.S. company will be considered a passive foreign investment company, or PFIC, for U.S. federal income tax purposes for any taxable year in which (1) 75% or more of its gross income consists of passive income or (2) 50% or more of the average quarterly value of its assets is attributable to assets that produce, or are held for the production of, passive income. For purposes of these tests, passive income generally 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.

There can be no assurance that we will not be considered a PFIC in any past, current or future taxable year, and based on the nature and composition of our income, assets, activities and market capitalization, it is likely that we will be a PFIC for our taxable year ended June 30, 2021 and in future taxable years. However, our PFIC status is based on an annual determination and may change from year to year. Our status as a PFIC will depend on the composition of our income and the composition and value of our assets, which may be volatile, from time to time. Our status may also depend, in part, on how quickly we utilize the cash we raise in any offering of our securities. Our U.S. counsel expresses no opinion regarding our conclusions or our expectations regarding our PFIC status.

If we are a PFIC for any taxable year during which a U.S. holder (as defined below in the section titled "Item 10E – Taxation") holds 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. We will continue to be treated as a PFIC with respect to such U.S. holder in all succeeding years during which the U.S. holder owns the ADSs, regardless of whether we continue to meet the PFIC test described above, unless the U.S holder makes a valid and timely qualified electing fund (QEF) or mark-to-market election, or makes a deemed

sale election once we cease to be a PFIC; however, we do not currently intend to provide the information necessary for a U.S holder to make a QEF election. 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 “Item 10E—Taxation.”

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

If a U.S. holder is treated as owning, (directly, indirectly or constructively,) at least 10% of the value or voting power of our ordinary shares or ADSs, such U.S. holder may be treated, for U.S. federal income tax purposes, as a “United States shareholder” with respect to each “controlled foreign corporation” in our group, if any. Because our group includes a U.S subsidiary (Opthea US Inc.), certain of our current and future non-U.S. subsidiaries will be treated as controlled corporations, regardless of whether we are treated as a controlled foreign corporation. A United States shareholder of a controlled foreign corporation may be required to annually report and include in its U.S. taxable income its pro rata share of “Subpart F income,” “global intangible low-taxed income” and investments in U.S. property by controlled foreign corporations, regardless of whether we make any distributions. An individual that is a United States shareholder with respect to a controlled foreign corporation generally would not be allowed certain tax deductions or foreign tax credits that would be allowed to a United States shareholder that is a U.S. corporation. We cannot provide any assurances that we will furnish to any United States shareholder information that may be necessary to comply with the reporting and payment obligations described above. Failure to comply with such obligations may subject a United States shareholder to significant monetary penalties and stall the beginning of the statute of limitations period for relevant U.S. federal income tax returns. U.S. holders should consult their tax advisors regarding the potential application of these rules to their investment in the ADSs.

Future changes to tax laws could materially adversely affect our company and reduce net returns to our shareholders.

Our tax treatment is subject to the enactment of, or changes in, tax laws, regulations and treaties, or the interpretation thereof, tax policy initiatives and reforms under consideration and the practices of tax authorities in jurisdictions in which we operate, including those related to the Organization for Economic Co-Operation and Development’s Base Erosion and Profit Shifting Project, the European Commission’s state aid investigations and other initiatives. 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. We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our financial position and overall or effective tax rates in the future in countries where we have operations, reduce post-tax returns to our shareholders, and increase the complexity, burden and cost of tax compliance.

Tax authorities may disagree with our position and conclusions regarding certain tax positions, 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, 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 arrangement 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, in which case, we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable.

General Risk Factors

We may be subject to securities litigation, which is expensive and could divert management’s attention.

The market price of the ordinary shares or ADSs may be volatile and, in the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial

costs and divert our management's attention from other business concerns, which could seriously harm our business.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, the price of the ADSs and their trading volume could decline.

The trading market for the ADSs depends in part on the research and reports that securities or industry analysts publish about us or our business. As a public listed company in Australia since 1985, our equity securities are currently subject to coverage by a number of analysts. If fewer securities or industry analysts cover our company, the trading price for the ADSs could be negatively impacted. If one or more of the analysts who covers us downgrades our equity securities or publishes incorrect or unfavorable research about our business, the price of the ADSs would likely decline. If one or more of these analysts ceases coverage of our company or fails to publish reports on us regularly, or downgrades our securities, demand for the ADSs could decrease, which could cause the price of the ADSs or their trading volume to decline.

We depend on our information technology systems and those of our third-party collaborators, service providers, contractors or consultants. Our internal computer systems, or those of our third-party collaborators, service providers, contractors or consultants, may fail or suffer security breaches, disruptions, or incidents, which could result in a material disruption of our development programs or loss of data or compromise the privacy, security, integrity or confidentiality of sensitive information related to our business and could harm our reputation, business, financial condition or results of operations.

In the ordinary course of our business, we collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information. Our internal technology systems and infrastructure, and those of our current or future third-party collaborators, service providers, contractors and consultants are vulnerable to damage from computer viruses, unauthorized access or use resulting from malware, natural disasters, terrorism, war and telecommunication and electrical failures, denial-of-service attacks, cyber-attacks or cyber-intrusions over the Internet, hacking, phishing and other social engineering attacks, persons inside our organizations (including employees or contractors), loss or theft, or persons with access to systems inside our organization. Attacks on information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and they are being conducted by increasingly sophisticated and organized non-U.S. governments, groups and individuals with a wide range of motives and expertise. For example, in June 2020, a coordinated cyber security attack targeted Australian government entities and companies. In addition to extracting or accessing sensitive information, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the security, confidentiality, integrity and availability of information. The prevalent use of mobile devices that access sensitive information also increases the risk of data security incidents which could lead to such sensitive information (which may include confidential information, other intellectual property or personal information) being subject to unauthorized access or otherwise compromised. While to our knowledge we have not experienced any material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations or the operations of third-party collaborators, service providers, contractors and consultants, it could result in a material disruption of our development programs and significant reputational, financial, legal, regulatory, business or operational harm. The costs to us to mitigate, investigate and respond to potential security incidents, breaches, disruptions, network security problems, bugs, viruses, worms, malicious software programs and security vulnerabilities could be significant, and while we have implemented security measures to protect our data security and information technology systems, our efforts to address these problems may not be successful, and these problems could result in unexpected interruptions, delays, cessation of service and other harm to our business and our competitive position.

For example, the loss of clinical trial data from completed, ongoing or planned clinical trials for our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any real or perceived security breach affects our systems (or those of our third-party collaborators, service providers, contractors or consultants), or results in the loss of or accidental, unlawful or unauthorized access to, use of, release of, or other processing of personal information or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed. Such a breach may require notification to governmental agencies, the media or individuals pursuant to various non-U.S. domestic (federal and state) privacy and security laws, if applicable, including HIPAA, as amended by HITECH, and its implementing rules and regulations, as well as regulations promulgated by the Federal Trade Commission and state breach notification laws. In addition,

our liability insurance may not be sufficient in type or amount to cover us against all losses and claims related to security breaches, cyberattacks and other related incidents.

Any failure or perceived failure by us or any third-party collaborators, service providers, contractors or consultants to comply with our privacy, confidentiality, data security or similar obligations, or any data security incidents or other security breaches that result in the accidental, unlawful or unauthorized access to, use of, release of, processing of, or transfer of sensitive information, including personal information, may result in negative publicity, harm to our reputation, governmental investigations, enforcement actions, regulatory fines, litigation or public statements against us, could cause third parties to lose trust in us or could result in claims by third parties, including those that assert that we have breached our privacy, confidentiality, data security or similar obligations, any of which could harm our reputation, business, financial condition or results of operations.

To the extent we maintain individually identifiable health information, we could be subject to fines and penalties (including civil and criminal) under HIPAA for any failure by us or our business associates to comply with HIPAA's requirements. Moreover, data security incidents and other security breaches can be difficult to detect, and any delay in identifying them may lead to increased harm. While we have implemented data security measures intended to protect our information, data, information technology systems, applications and infrastructure, there can be no assurance that such measures will successfully prevent service interruptions or data security incidents.

Our insurance policies are expensive and only protect us from some business risks, leaving us exposed to significant uninsured liabilities.

We do not carry insurance for all categories of risk that our business may encounter. We believe that we maintain insurance customary for businesses of our size and type, including clinical trial liability insurance. However, there are types of losses we may incur that cannot be insured against or that we believe are not economically reasonable to insure. Moreover, any loss incurred could exceed policy limits and policy payments made to us may not be made on a timely basis. Such losses could negatively affect our business prospects, results of operations, cash flows and financial condition. We do not know if our current levels of coverage are adequate or if we will be able to obtain insurance with adequate levels of coverage in the future, if at all. Any significant uninsured liability may require us to pay substantial amounts, which could negatively impact our financial position and results of operations.

If we fail to implement and maintain an effective system of internal control over financial reporting, we may be unable to accurately report our results of operations, meet our reporting obligations or prevent fraud, and investor confidence in our company and the market price of the ADSs may be negatively impacted.

Section 404(a) of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, requires that our management assess and report annually on the effectiveness of our internal controls over financial reporting and identify any material weaknesses in our internal controls over financial reporting. While we have not identified any material weaknesses in our internal controls over financial reporting as of June 30, 2021, and have remediated prior material weaknesses, if in the future, we fail to maintain effective internal controls, as such standards are modified, supplemented or amended from time to time, we may not be able to ensure that we can conclude on an ongoing basis that we have effective internal controls over financial reporting in accordance with Section 404(a).

The presence of material weaknesses could result in financial statement errors which, in turn, could lead to errors in our financial reports or delays in our financial reporting, which could require us to restate our operating results or result in our auditors issuing a qualified audit report. In order to establish and maintain effective disclosure controls and procedures and internal controls over financial reporting, we will need to expend significant resources and provide significant management oversight. Developing, implementing and testing changes to our internal controls may require specific compliance training of our directors and employees, entail substantial costs in order to modify our existing accounting systems, take a significant period of time to complete and divert management's attention from other business concerns. These changes may not, however, be effective in establishing and maintaining adequate internal controls.

If either we are unable to conclude that we have effective internal controls over financial reporting or our independent auditors are unwilling or unable to provide us with an unqualified report on the effectiveness of our internal controls over financial reporting as required by Section 404(b) of the Sarbanes-Oxley Act, investors may lose confidence in our operating results, the price of the ADSs could decline and we may be subject to litigation or regulatory enforcement actions. In addition, if we are unable to meet the requirements of Section 404 of the Sarbanes-Oxley Act, we may not be able to remain listed on Nasdaq.

Item 4. Information on the Company

4A. History and Development of Opthea Limited

We were incorporated under the laws of Australia in 1984 under the name Circadian Technologies Limited. In 1985, we completed an initial public offering of our ordinary shares and the listing of our ordinary shares on the Australian Securities Exchange, or the ASX. In December 2015, we changed the name of our company to Opthea Limited. Our headquarters and registered offices are located at Suite 0403, Level 4, 650 Chapel Street, South Yarra, VIC 3141, Australia. Our telephone number is +61 3 9826 0399. Our agent for service of process in the United States is Corporation Service Company, located at 1180 Avenue of the Americas, Suite 210, New York, NY 10036. Our website address is www.opthea.com. The reference to our website is an inactive textual reference only and information contained in, or that can be assessed through, our website is not part of this annual report. The SEC maintains a website (www.sec.gov) that contains reports, proxy and information statements and other information regarding registrants, such as us, that file electronically with the SEC.

4B. Business Overview

We are a clinical stage biopharmaceutical company developing a novel therapy for the treatment of highly prevalent and progressive retinal diseases. We are developing our Phase 3-ready product candidate, OPT-302, a biologic designed to inhibit VEGF-C and VEGF-D, to complement VEGF-A inhibitors for the treatment of ophthalmic diseases. Anti-VEGF-A therapies represent the standard of care for wet age-related macular degeneration, or AMD, and other retinal diseases; however, there remains a significant unmet medical need as many patients do not adequately respond to these treatments. As the only biologic inhibitor of VEGF-C and VEGF-D in clinical development for ophthalmology, OPT-302 differs from standard of care therapies and when administered in combination with a VEGF-A inhibitor, is designed to achieve broader inhibition of the vascular endothelial growth factor, or VEGF, family and target a mechanism of clinical resistance to improve visual acuity. Our lead indication for OPT-302 combination therapy is wet AMD, a chronic, progressive disease and the leading cause of vision loss for individuals over the age of 50. In a 366-patient Phase 2b clinical trial for the treatment of wet AMD, 2.0 mg OPT-302, in combination with a standard of care anti-VEGF-A therapy, ranibizumab (Lucentis), met the primary endpoint of a statistically significant superior mean gain in visual acuity over ranibizumab monotherapy at week 24. We intend to initiate two pivotal Phase 3 clinical trials in treatment-naive patients with wet AMD to evaluate the efficacy and safety of OPT-302 in combination with anti-VEGF-A therapies compared to anti-VEGF-A monotherapy in the first half of 2021. We expect to report topline data from these Phase 3 clinical trials in 2023. In addition to our clinical trials in wet AMD, we have observed evidence of improved clinical outcomes in a Phase 1b/2a clinical trial of OPT-302 in combination with another standard of care anti-VEGF-A therapy, aflibercept (Eylea), in patients with treatment-refractory diabetic macular edema, or DME. We retain worldwide rights to develop and commercialize OPT-302 for the treatment of wet AMD and DME and believe that the novel treatment mechanism of OPT-302 has the potential to provide therapeutic benefit for other progressive eye diseases.

Wet AMD is a rapidly progressing disease with loss of central vision developing over a period of weeks to months in which abnormal new blood vessels form in the back of the eye in a process called choroidal neovascularization, or CNV. These newly formed vessels are highly permeable, leaking exudate leading to fluid accumulation and retinal lesion formation. This, in turn, adversely affects sensory cells in the retina and if left untreated, results in rapid loss of visual acuity.

Wet AMD affects approximately one million people in the United States and 2.5 million people in Europe. The standard of care for wet AMD and other ocular neovascular diseases is the administration of monotherapies that primarily inhibit VEGF-A. These therapeutic agents, which include ranibizumab and aflibercept, prevent VEGF-A molecules from binding to, and activating, VEGF receptors and thereby inhibit the formation and permeability of blood vessels. As the risk of developing wet AMD increases with age, it is predicted that the overall aging of the population will result in a significant increase in the number of wet AMD cases, both in the United States and worldwide. Many wet AMD patients also experience suboptimal clinical responses despite receiving one or both of the leading standard of care treatments ranibizumab and aflibercept, which had combined annual worldwide sales of over US$11.9 billion in 2019. In addition, nearly half of wet AMD patients are treated with off-label bevacizumab as a lower cost alternative anti-VEGF-A therapy. As a result, we believe there is a significant and expanding market opportunity for novel therapies that can improve vision in patients with wet AMD, which has the potential to lead to sales greater than the combined annual sales of ranibizumab and aflibercept.