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

FORM 6-K

REPORT OF FOREIGN PRIVATE ISSUER
PURSUANT TO RULE 13a-16 OR 15d-16
UNDER THE SECURITIES EXCHANGE ACT OF 1934

For the Month of September 2018

Commission File Number: 001-38217

Nightstar Therapeutics plc
(Translation of registrant's name into English)

10 Midford Place, 2nd Floor
London W1T 5BJ United Kingdom
(Address of principal executive office)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F:

☒ Form20-F ☐ Form 40-F

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1): ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7): ☐

Nightstar Therapeutics plc (the "Company") is providing the risk factors attached to this Report of Foreign Private Issuer on Form 6-K as Exhibit 99.1 to update and supersede the risk factors contained in its periodic reports filed with the U.S. Securities and Exchange Commission (the "SEC") pursuant to the Securities Exchange Act of 1934, as amended, including those under the heading "Item 3.D. Risk Factors" in its Annual Report on Form 20-F for the year ended December 31, 2017, filed with the SEC on April 3, 2018.

Exhibit	Description
99.1	Risk Factors

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

NIGHTSTAR THERAPEUTICS PLC

Date: September 25, 2018

By: /s/ Bryan Yoon
Name: Bryan Yoon
Title: General Counsel and Secretary

Exhibit 99.1

RISK FACTORS

Nightstar Therapeutics plc is filing information for the purposes of updating and superseding the risk factor disclosure contained in its prior public filings, including those previously set forth in Part I, Item 3A, "Risk Factors" of its Annual Report on Form 20-F for the year ended December 31, 2017, filed with the Securities and Exchange Commission, or the SEC, on April 3, 2018. Any reference herein to "we," "us," "our," or similar term shall refer to Nightstar Therapeutics plc and its subsidiaries.

Investing in our ADSs involves a high degree of risk. Before you invest in our ADSs, you should carefully consider the following risks, as well as general economic and business risks. Any of the following risks could have a material adverse effect on our business, operating results and financial condition and cause the trading price of our ADSs to decline, which would cause you to lose all or part of your investment. When determining whether to invest, you should also refer to the other information contained or incorporated by reference in this Report on Form 6-K. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also adversely affect our business.

Risks Related to Our Financial Position and Need for Capital

We have incurred net losses since inception and may never achieve or maintain profitability.

Since our inception in May 2013, we have incurred significant net losses. We have incurred recurring losses since our inception, including net losses of $8.1 million and $4.2 million for the three months ended June 30, 2018 and 2017, respectively, and $22.5 million and $7.7 million for the six months ended June 30, 2018 and 2017, respectively. Our net losses were $29.7 million, $12.2 million and $13.6 million for the years ended December 31, 2017, 2016 and 2015, respectively. In addition, as of June 30, 2018 and December 31, 2017, we had an accumulated deficit of $84.5 million and $62.0 million, respectively. We have devoted substantially all of our efforts to research and development of our lead product candidates as well as to manufacturing our product candidates, organizing and staffing our company, raising capital, and establishing our intellectual property portfolio. We expect that it could be several years, if ever, before we have a commercialized product candidate. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. These net losses will adversely impact our shareholders' equity and net assets and may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially if, and as, we:

- continue research and development of our retinal gene therapy product candidates, including our STAR Phase 3 registrational trial for NSR-REP1, our ongoing Phase 1/2 clinical trial for NSR-RPGR and the advancement of our preclinical product candidates;
- initiate clinical trials and preclinical studies for any additional product candidates that we may pursue in the future;
- prepare a potential future biologics license application, or BLA, and marketing authorization application, or MAA, for each of our retinal gene therapy product candidates;
- manufacture our product candidates in accordance with current good manufacturing practices, or cGMP, for clinical trials or potential commercial sales;
- establish and validate contracted commercial-scale cGMP manufacturing facilities;
- further develop our pipeline of retinal gene therapy product candidates;
- establish a sales, marketing and distribution infrastructure to commercialize any product candidate for which we may obtain marketing approval;
- develop, maintain, expand and protect our intellectual property portfolio;
- acquire or in-license other product candidates and technologies;
- secure, maintain or obtain freedom to operate for any in-licensed technologies and products;

- expand our operational, financial and management systems and personnel, including personnel to support our clinical development, manufacturing and commercialization efforts and our operations as a public company in the United States, Europe and potentially other jurisdictions; and
- continue to operate as a public company.

We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly, annual or longer-term basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company also could cause you to lose all or part of your investment.

We will need additional funding to complete the development of our product candidates, which may not be available on acceptable terms, if at all. Failure to raise capital when needed may force us to delay, limit or terminate certain of our product development and commercialization efforts or other operations.

As of June 30, 2018, we had cash, cash equivalents and marketable securities of $111.4 million. We believe we have sufficient cash and cash equivalents to fund our operating expenses and capital expenditure requirements for at least the next 12 months. We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for our product candidates, we expect to incur significant expenses related to product sales, marketing, manufacturing and distribution. Furthermore, we expect to incur additional costs associated with operating as a public company. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of laboratory testing, manufacturing, and preclinical and clinical development for our current and future product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- our ability to establish and maintain collaborations and license agreements on favorable terms, if at all;
- the costs of expanding our facilities to accommodate our expected growth in personnel;
- the extent to which we acquire or in-license other product candidates and technologies or establish collaboration, distribution or other marketing arrangements for our product candidates;
- the costs, timing and outcome of potential future commercialization activities, including manufacturing, marketing, sales and distribution for our product candidates for which we receive marketing approval;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the sales price and availability of adequate third-party coverage and reimbursement for our product candidates, if and when approved; and
- the costs of operating as a public company in the United States.

Developing product candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete. We may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our product revenues, if any, will be derived from or based on sales of product candidates that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives.

Adequate additional financing may not be available to us on acceptable terms, if at all. To the extent that additional capital is raised through the issuance of equity or equity-linked securities, the issuance of those securities could

result in substantial dilution for our current shareholders and the terms of any future issuance may include liquidation or other preferences that adversely affect the rights of our current shareholders. Debt financing, if available, may involve agreements that include covenants restricting our operations or our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. Any debt or additional equity financing that we raise may contain terms that are not favorable to us or our shareholders. If we raise additional funds through collaborations, strategic alliances, or licensing arrangements with third parties, it may be necessary to relinquish some rights to our technologies, future revenue streams, research programs or our product candidates, or to grant licenses on terms that are not favorable to us. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our ADSs to decline and existing shareholders may not agree with our financing plans or the terms of such financings.

If we are unable to obtain adequate funding on a timely basis or on terms that are favorable to us, we may be required to significantly delay, limit, reduce or terminate our product development or future commercialization efforts or to grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves; be unable to expand our operations; or be unable to otherwise capitalize on our business opportunities, as desired, which could harm our business and potentially cause us to discontinue operations.

Our limited operating history may make it difficult to evaluate the success of our business to date and to assess our future viability.

Since our inception, we have devoted substantially all of our resources to research and development of our lead product candidates as well as to manufacturing our product candidates, organizing and staffing our company, raising capital, and establishing our intellectual property portfolio. We have not yet demonstrated our ability to successfully complete Phase 3 or other pivotal clinical trials, obtain regulatory approvals, manufacture a product suitable for commercialization or arrange for a third party to do so on our behalf or conduct sales and marketing activities necessary for successful product commercialization. Additionally, we are not profitable and have incurred losses in each year since our inception, and we expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history. We are in the process of transitioning from a company with a research focus to a company that is also capable of supporting later-stage clinical development and potentially commercial activities. We may not be successful in such a transition.

Risks Related to the Development of our Product Candidates

Our gene therapy product candidates are based on novel technologies, which makes it difficult to predict the timing and costs of development and of subsequently obtaining regulatory approval, and only a limited number of gene replacement therapy products have been approved by regulatory agencies to date.

We have concentrated our research and development efforts on NSR-REP1 for the treatment of choroideremia, or CHM, and NSR-RPGR for the treatment of X-linked retinitis pigmentosa, or XLRP, our two most advanced product candidates. Because we are developing product candidates for the treatment of inherited retinal diseases for which there are no or limited therapies and/or treatments, and for which there is little clinical trial experience, there is an increased risk that the FDA, EMA, or other regulatory authorities may not consider our clinical trials to be sufficient for marketing approval. Although more than 250 genes that play a role in inherited retinal diseases have been identified, we believe the number of targets currently in clinical development to be only in the low double-digits.

The product specifications and the clinical trial requirements of the FDA, EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of such product candidate. The regulatory approval process for novel product candidates such as ours is unclear and may be lengthier and more expensive than the process for other, better-known or more extensively studied product candidates. For example, the FDA generally requires multiple well-controlled clinical trials to provide the evidence of effectiveness necessary to support a BLA, although FDA guidance provides that reliance on a single pivotal trial may be appropriate if the trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potential serious outcome, and where confirmation of the result in a second trial would be practically or ethically

impossible. The FDA confirmed this position in our pre-IND meeting with them in 2015. We intend that our STAR Phase 3 registrational trial will be the only Phase 3 trial necessary to support a BLA for NSR-REP1, but there can be no assurance that the FDA will accept this single trial as sufficient to demonstrate substantial evidence of effectiveness of NSR-REP1 under its guidelines.

Regulatory requirements governing gene and cell therapy products have changed frequently and may continue to change in the future. The FDA has established the Office of Cellular, Tissue and Gene Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise the CBER in its review. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the National Institutes of Health, or NIH, are also potentially subject to review by the NIH's Office of Biotechnology Activities' Recombinant DNA Advisory Committee, or the RAC. Even though the FDA decides whether individual gene therapy protocols may proceed, the RAC public review process, if undertaken, can delay the initiation of a clinical trial, even if the FDA has reviewed the trial design and details and permitted its initiation. Conversely, the FDA may place an Investigational New Drug application, or IND, on a clinical hold even if the RAC has provided a favorable review or an exemption from in depth, public review. NIH-funded institutions also need to have their institutional biosafety committee, or IBC, as well as their institutional review board, or IRB, review proposed clinical trials to assess the safety of the trial.

These regulatory review committees and advisory groups, and the new guidelines they promulgate, may lengthen the regulatory review process, require us to perform additional preclinical studies or clinical trials, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of our current or future product candidates or lead to significant post-approval limitations or restrictions. While the NIH and FDA have recently issued new draft guidance for the development of gene therapies and proposed new rules that would streamline certain requirements to which gene therapies are currently subject, it remains to be seen as to whether such initiatives will ultimately increase the speed of drug development in gene therapies such as our product candidates.

As we advance our product candidates, we will be required to consult with these regulatory and advisory groups and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects would be harmed. Even if our product candidates are approved, we expect that the FDA will require us to submit follow-up data regarding our clinical trial subjects for a number of years after approval. If this follow-up data shows negative long-term safety or efficacy outcomes for these patients, the FDA may revoke its approval or change the label of our products in a manner that could have an adverse impact on our business.

In addition, adverse developments in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of our product candidates. Similarly, the EMA and competent authorities within the European Union Member States may issue new guidelines that could affect the development and marketing authorization for gene therapy products and require that we comply with these new guidelines. The EMA and agencies at both the federal and state level in the United States have expressed an interest in further regulating new biotechnologies, including gene therapy. In addition, gene therapy products would usually be considered genetically-modified organism, or GMO, products and are regulated as such. This is particularly significant for development products that have not received marketing authorizations. In such cases, designation of the type of GMO product and subsequent handling and disposal requirements can vary across European Union Member States. Addressing each specific country requirement and obtaining approval to commence a clinical trial in these countries could result in delays in starting, conducting, or completing a clinical trial. Similar issues could be faced in other regions of the world. Although numerous companies are currently advancing gene therapy products through clinical trials, to our knowledge, only two gene therapy products, uniQure N.V.'s Glybera (which has since been withdrawn from the market) and GlaxoSmithKline's Strimvelis, have received marketing authorization from the European Commission, and one gene replacement therapy product, Spark Therapeutics' Luxturna, has been approved by the FDA. While Luxtura has not yet received marketing authorization from the European Commission, it has received a positive opinion from the Committee for Medicinal Products for Human Use, or CHMP.

As a result, it is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for NSR-REP1 in either the United States or the European Union or how long it will take to receive regulatory approval for and commercialize our other product candidates. Approvals by the EMA may not be indicative of what the FDA may require for approval and vice versa.

We may encounter substantial delays or difficulties in our clinical trials.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates. Clinical testing is expensive, time-consuming and uncertain as to outcome. We have limited experience with clinical trials. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with the FDA, EMA or other regulatory authorities on trial design;
- delays in initiating trials due to any additional review that is required by RAC, if applicable;
- delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- delays in opening clinical trial sites or obtaining required IRB or independent ethics committee approval at each clinical trial site;
- our decision or the requirement of regulators or IRBs to suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements, a finding that the participants are being exposed to unacceptable health risks, or the imposition of a clinical hold as a result of a serious adverse event or after an inspection of our clinical trial operations or clinical trial sites;
- delays in recruiting suitable patients to participate in our future clinical trials;
- failure by us, any CROs we engage or any other third parties to adhere to clinical trial or regulatory requirements;
- failure by us, any CROs we engage or any other third parties to perform in accordance with Good Clinical Practice, or GCP, cGMPs, or applicable regulatory guidelines in the United States, the European Union and other international markets;
- failure by physicians to adhere to delivery protocols leading to variable results;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical trial sites, including delays by third parties with whom we have contracted to perform certain of those functions;
- insufficient or inadequate supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates;
- delays in having patients complete participation in a clinical trial or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a clinical trial at a rate higher than we anticipate;
- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;
- receipt of negative or inconclusive clinical trial results;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits;

- occurrence of serious adverse events in clinical trials of the same class of agents conducted by other sponsors; and
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;

We expect our STAR Phase 3 trial in CHM to be fully enrolled by the first half of 2019. We are also conducting a Phase 1/2 clinical trial known as the XIRIUS trial with our second product candidate, NSR-RPGR, for the treatment of X-linked retinitis pigmentosa, or XLRP. We presented preliminary efficacy and safety data from the ongoing dose escalation study of NSR-RPGR in the XIRIUS trial at a medical conference in September 2018. Also, we expect to initiate the enrollment of an expansion study in the XIRIUS trial during the fourth quarter of 2018. The expansion study in the XIRIUS trial is intended to enroll approximately 30 patients at a therapeutic dose informed by the dose escalation study and is anticipated to include a low-dose control group of approximately 15 patients. Based on the current schedule, we expect to announce preliminary data from the expansion study in the XIRIUS trial in mid-2019. One-year follow-up data from each of the dose escalation study and the expansion study in the XIRIUS trial is expected in the second half of 2019 and in 2020, respectively. Our anticipated timelines for these and other trials and studies on our product candidates may be subject to delays due to factors such as those discussed above.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory, development and commercialization milestones and royalties. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

We may fail to demonstrate safety and efficacy of our product candidates to the satisfaction of applicable regulatory authorities.

If the results of our STAR Phase 3 registrational trial of NSR-REP1, our XIRIUS Phase 1/2 trial of NSR-RPGR in XLRP or future trials for our other product candidates are inconclusive or do not demonstrate the efficacy of our product candidates, or if there are safety concerns or serious adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements;
- be subject to changes in the way the product is administered;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw or suspend their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy, or REMS;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Our development costs will increase if we experience delays in testing or marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin or progress as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical study or clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates.

Success in preclinical studies or clinical trials may not be indicative of results in future clinical trials.

Results from previous preclinical studies or clinical trials are not necessarily predictive of future clinical trial results, and interim results of a clinical trial are not necessarily indicative of final results. Our product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through initial clinical trials or preliminary stages of clinical trials. For example, we have limited safety and efficacy data for the use of NSR-REP1, NSR-RPGR or any of our other product candidates in humans. The clinical trial process may fail to demonstrate that NSR-REP1, NSR-RPGR or any of our other product candidates is safe and effective for indicated uses. This failure would cause us to abandon further clinical development of NSR-REP1, NSR-RPGR or our other product candidates.

Success in preclinical testing and early clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. Frequently, product candidates that have shown promising results in early clinical trials have subsequently suffered significant setbacks in later clinical trials. To date, our clinical trials have involved small patient populations and because of the small sample size, the interim results of these clinical trials may be subject to substantial variability and may not be indicative of either future interim results or final results. In addition, the design of a clinical trial, such as endpoints, inclusion and exclusion criteria, statistical analysis plans, data access protocols and trial sizing, 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. Due to ethical concerns of utilizing sham surgery, our clinical trials are conducted on an open-label basis. While we aim to have adequate quality controls, open-label trials are inherently subject to greater risk of bias than double-blinded, placebo-controlled trials. Furthermore, as we are exploring new disease areas without any approved treatments, we may need to qualify new and unproven endpoints as we are continuing the development of our product candidates, which may increase uncertainty.

We also have limited experience designing clinical trials and may be unable to design and execute a clinical trial to support regulatory approval. There is a high failure rate for drugs and biologic products proceeding through clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including due to changes in regulatory policy during the period of our product candidate development. Any such failures or delays could negatively impact our business, financial condition, results of operations and prospects.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. However, patient recruitment may be difficult and actual enrollment may differ from our expected timelines. The timing of our clinical trials depends on our ability to recruit patients to participate, as well as completion of required follow-up periods. If patients are unwilling to enroll in our gene therapy clinical trials because of negative publicity from adverse events related to the biotechnology or gene therapy fields, competitive clinical trials for similar patient populations, clinical trials in products employing our vector or our platform or for other reasons, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of our product candidates may be delayed. These delays could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of clinical trials altogether.

Our current product candidates are being developed to treat rare conditions, which are generally defined as having a patient population of fewer than 200,000 individuals in the United States. For example, the prevalence of CHM is estimated to be one in 50,000 people, implying a total population of approximately 13,000 in the United States and the five major European markets, and the prevalence of XLRP is approximately one in 40,000 people, implying a total population of approximately 17,000 in the same regions. We may not be able to initiate or continue clinical

trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA, EMA or other regulatory authorities. Also, our natural history studies may not provide any advantage to us in enrolling patients in our late-stage clinical trials. As a result, we may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics, to complete our clinical trials in a timely manner. Patient enrollment can be affected by many factors, including:

- size of the patient population and process for identifying patients;
- perceived risks and benefits of our product candidates or gene therapy treatment in general;
- availability of competing therapies and clinical trials;
- design of the trial protocol, including eligibility and exclusion criteria for our clinical trials;
- severity of the disease under investigation;
- availability of genetic testing for potential patients;
- proximity and availability of clinical trial sites for prospective patients;
- ability to obtain and maintain patient consent;
- patient drop-outs prior to completion of clinical trials;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

Our ability to successfully initiate, enroll and complete clinical trials in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with CROs and physicians;
- different standards for the conduct of clinical trials;
- absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;
- inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

As described above, we expect our STAR Phase 3 trial in CHM to be fully enrolled by the first half of 2019. We are also conducting a Phase 1/2 clinical trial with our second product candidate, NSR-RPGR, for the treatment of XLRP. We expect to initiate the enrollment of the expansion study in the XIRIUS trial during the fourth quarter of 2018. The expansion study in the XIRIUS trial is intended to enroll approximately 30 patients at a therapeutic dose informed by the dose escalation study and is anticipated to include a low-dose control group of approximately 15 patients. Our anticipated timelines for these and other trials and studies on our product candidates may be subject to delays in enrollment. If we have difficulty enrolling a sufficient number of patients or finding additional clinical trial sites to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which could have an adverse effect on our business, financial condition, results of operations and prospects.

Our product candidates and the process for administering our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following any potential marketing approval.

During the conduct of clinical trials, patients report changes in their health, including illnesses, injuries and discomforts, to their study doctor. Often, it is not possible to determine whether the product candidate being studied caused these conditions. Various illnesses, injuries and discomforts have been reported from time to time during clinical trials of our product candidates. Regulatory authorities may draw different conclusions or require additional testing to confirm these determinations.

In addition, it is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of these product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by patients. Many times, side effects are only detectable after investigational products are tested in large-scale, Phase 3 clinical trials or, in some cases, after they are made available to patients on a commercial scale after approval. If additional clinical experience indicates that our product candidates cause serious or life-threatening side effects, the development of our product candidates may fail or be delayed, or, if the product candidate has received regulatory approval, such approval may be revoked, which would harm our business, prospects, operating results and financial condition.

There have been several significant adverse side effects in gene therapy treatments in the past, including reported cases of leukemia and death seen in other clinical trials using other vectors. While new recombinant vectors have been developed to reduce these side effects, gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. There also is the potential risk of delayed adverse events following exposure to gene therapy products due to persistent biologic activity of the genetic material or other components of products used to carry the genetic material.

Possible adverse side effects that could occur with treatment with gene therapy products include an immunologic reaction early after administration which, while not necessarily adverse to the patient's health, could substantially limit the effectiveness of the treatment. In previous clinical trials involving adeno-associated virus, or AAV, vectors for gene therapy, some patients experienced the development of a T-cell response, whereby after the vector is within the target cell, the cellular immune response system triggers the removal of transduced cells by activated T-cells. If our vectors demonstrate a similar effect, we may decide or be required to halt or delay further clinical development of our product candidates or withdraw the product from the market post-approval. In addition to any potential side effects caused by our product candidates, the administration process or related procedures also can cause adverse side effects. If any such adverse events occur, our clinical development or clinical trials could be suspended or terminated, and our commercial efforts could be materially and adversely affected. Serious adverse events in our clinical trials, or other clinical trials involving gene therapy products or our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could also result in increased or more stringent regulation or oversight, unfavorable public perception, potential delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

As of the date of this Report on Form 6-K, available clinical data from the 32 treated patients in the completed ISTs indicates that NSR-REP1 was well tolerated. The safety profile in the completed ISTs is consistent with that of surgical vitrectomy procedures generally and what has been observed in clinical trials of other ocular gene therapies. Adverse events of varying severity and duration related to the vitrectomy procedure or drug have been observed in the completed ISTs such as retinal changes, intraocular inflammation and visual disturbances, which generally resolved within one week after surgery. The adverse events observed in our ongoing clinical trials of NSR-REP1 have also generally been consistent with the adverse events seen in the completed ISTs and other ocular gene therapy trials.

Two serious adverse events were observed in patients treated with NSR-REP1 in our completed clinical trials and investigator sponsored trials, or ISTs. One of these events was not ocular in nature and were determined to be unrelated to treatment. The other event was intraocular inflammation, requiring additional treatment with oral steroids. This transient inflammation was determined to be possibly related to treatment with NSR-REP1.

In September 2018, we announced that positive preliminary safety and efficacy data of NSR-RPGR from the dose escalation study in the Phase 1/2 XIRIUS trial was presented at the EURETINA 2018 Congress. While no serious adverse events related to treatment were reported and no early discontinuations or dose limiting toxicity were observed, mild drug-related inflammation that potentially dampened efficacy was seen in the treated eyes of cohorts 4 and 5.

If in the future we are unable to demonstrate that such adverse events were caused by the administration process or related procedures, the FDA, EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Even if we are able to demonstrate that any serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the clinical trial. Moreover, if we elect or are required to delay, suspend or terminate any clinical trial of any of our product candidates, the commercial prospects of such product candidate may be harmed and our ability to generate product revenues from such product candidate may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates, and may harm our business, financial condition and prospects.

Additionally, if we or others later identify undesirable side effects caused by any of our product candidates, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product candidate;
- regulatory authorities may require additional warnings on the label;
- we may be required to change the way a product candidate is administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates.

Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience and could experience production problems that result in delays in our development or commercialization programs.

We have limited experience manufacturing our product candidates. We may be unable to produce commercial materials or meet demand to support a commercial launch for our product candidates. Any such failure could delay or prevent the development of our product candidates and would have a negative impact on our business, financial condition and results of operations.

The manufacturing processes we use to produce NSR-REP1, NSR-RPGR and our other product candidates are complex, require substantial expertise and capital investment and have not yet been validated for commercial use. As a result, we may need to change our current manufacturing processes for our product candidates. There are no assurances that we will be able to produce sufficient quantities of our product candidates due to several factors, including equipment malfunctions, facility contamination, raw material shortages or contamination, natural disasters, disruption in utility services, human error or disruptions in the operations of our suppliers. We may also fail to produce adequate quantities of our product due to our failure to properly predict the demand for our product or the market size of our targeted indications.

Our product candidates require processing steps that are more complex than those required for most chemical pharmaceuticals. Moreover, unlike chemical pharmaceuticals, the physical and chemical properties of a biologic such as ours generally cannot be fully characterized. As a result, assays of the finished product may not be sufficient to ensure that the product will perform in the intended manner or that the dosing will be uniform in our products. Accordingly, we employ multiple steps to control our manufacturing process to assure that the process works and that our product candidates are made strictly and consistently in compliance with the process. Problems with the manufacturing process, including even minor deviations from the normal process, could result in product defects or manufacturing failures that result in lot failures, product recalls, product liability claims or insufficient inventory. We may encounter problems achieving adequate quantities and quality of clinical-grade or commercial-grade materials that meet FDA, EMA or other applicable standards or specifications with consistent and acceptable production yields and costs.

In addition, the FDA, EMA and other regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA, EMA or other regulatory authorities may require that we not distribute a lot until the agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in the product that could result in lot failures or product recalls. Lot failures or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects.

We presently contract with third parties for the manufacturing of our program materials. The use of contracted manufacturing and reliance on collaboration partners is relatively cost efficient and has eliminated the need for our direct investment in manufacturing facilities and additional staff early in development to date. Although we rely on contract manufacturers, we have personnel with manufacturing and quality experience to oversee our contract manufacturers. We expect third-party manufacturers to be capable of providing sufficient quantities of our materials to meet anticipated clinical trial scale demands, but there can be no assurance that all of our requirements will be satisfied.

As a result of the limited number of regulatory approvals for gene replacement products to date, the timeframe required for us to obtain approval for a cGMP gene therapy manufacturing facility is uncertain. We must supply all necessary documentation in support of a BLA or other MAA on a timely basis and must adhere to the FDA's and EMA's cGMP requirements before NSR-REP1, NSR-RPGR and our other product candidates can obtain marketing approval. In order to obtain approval, we will need to ensure that all of our processes, methods and equipment are compliant with cGMP, and perform extensive audits of contract laboratories, manufacturers and suppliers. Until recently, no cGMP gene therapy manufacturing facility in the United States had received approval from the FDA to manufacture an approved gene therapy product. We are subject to audits from FDA, EMA and other authorities that may result in observations of non-compliance from cGMP requirements.

Any contamination in our manufacturing process, shortages of raw materials or failure of any of our key suppliers to deliver necessary components could result in delays in our clinical development or marketing schedules.

Given the nature of biologics manufacturing, there is a risk of contamination. Any contamination could adversely affect our ability to produce product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage. Some of the raw materials required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could adversely affect our development timelines and our business, financial condition, results of operations and prospects.

Risks Related to Our Reliance on Third Parties

If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are important to our business.

We are party to several license agreements under which we in-license patent rights and other intellectual property related to our business, and we may enter into additional license agreements in the future. Our license agreements impose, and we expect that future license agreements will impose, various due diligence, milestone payment, royalty, insurance and other obligations on us. Any uncured material breach under these license agreements could result in our loss of rights to practice the patent rights and other intellectual property licensed to us under these agreements and could compromise our development and commercialization efforts for our current or future product candidates. See the section of our Annual Report on Form 20-F for the period ended December 31, 2017 titled "Item 4.B. Information on the Company—Business Overview—Collaborations and License Agreements" for a more detailed description of our current license agreements.

We rely, and expect to continue to rely, on third parties to conduct our preclinical studies and clinical trials. If these third parties do not successfully carry out their contractual duties or perform satisfactorily, including meeting expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates.

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators and third-party CROs, to conduct our preclinical studies and clinical trials properly and on time and to monitor and manage data for our ongoing preclinical and clinical programs. We rely on these parties for execution of our preclinical studies and clinical trials, and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for all of our product candidates in clinical development. We are also required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes.

Regulatory authorities enforce GCP requirements through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we fail to exercise adequate oversight over any of our CROs or if we or any of our CROs or other third parties performing services fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or other regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon a regulatory inspection of us or our CROs or other third parties performing services in connection with our clinical trials, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our future clinical trials will require a sufficient number of patients to evaluate the safety and effectiveness of our product candidates. Accordingly, if we or our third-party service providers fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical trials, which would delay the regulatory approval process. Failure to comply can also result in fines, adverse publicity, and civil and criminal sanctions.

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

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

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

Switching or engaging additional CROs involves additional cost and requires our management's time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays could occur, which could materially impact our ability to meet our desired clinical development timelines.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

We have engaged contract manufacturing organizations, or CMOs, to manufacture our product candidates such as NSR-REP1 and NSR-RPGR and to perform quality testing, and because we collaborate with various organizations and academic institutions for the advancement of our gene therapy platform, we must, at times, share our proprietary technology and confidential information, including trade secrets, with them. We seek to protect our proprietary technology, in part, by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our proprietary technology and confidential information or other unauthorized use or disclosure of such technology or information would impair our competitive position and may have an adverse effect on our business, financial condition, results of operations and prospects.

Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets by third parties. A competitor's discovery of our trade secrets or proprietary information would impair our competitive position and have an adverse impact on our business, financial condition, results of operations and prospects.

We utilize, and expect to continue to utilize, third parties to conduct our product manufacturing for the foreseeable future, and these third parties may not perform satisfactorily and may be difficult to replace.

We currently rely on CMOs for the manufacturing of clinical batches and intend to continue to rely on third parties to manufacture our preclinical study and clinical trial product supplies. Supply requirements for our clinical trials as well as current and future clinical requirements for NSR-REP1, NSR-RPGR and our other product candidates have been and will be manufactured by cGMP compliant third-party manufacturers. If these third-party manufacturers do not successfully carry out their contractual duties, meet expected deadlines or manufacture NSR-REP1, NSR-RPGR or our other product candidates in accordance with regulatory requirements or if there are disagreements between us and these third-party manufacturers, we will not be able to complete, or may be delayed in completing, the preclinical studies required to support future Investigational New Drug, or IND, submissions and the clinical trials required for approval of our product candidates. In such instances, we may need to enter into an appropriate replacement third-party relationship, which may not be readily available or available on acceptable terms or timeframes, which would cause additional delay or increased expense prior to the approval of NSR-REP1, NSR-RPGR or any of our other product candidates and would thereby have a negative impact on our business, financial condition, results of operations and prospects.

Under certain circumstances, our current CMOs are entitled to terminate their engagements with us. If we need to enter into alternative arrangements, it could delay our development activities. Our reliance on our CMOs for certain manufacturing activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations. If our current CMOs, or any future third-party manufacturers, do not successfully carry out their contractual duties, meet expected deadlines or manufacture our product candidates in accordance with regulatory requirements, or if there are disagreements between us and our CMOs or any future third-party manufacturers, we will not be able to complete, or may be delayed in completing, the preclinical studies required to support future IND submissions, the clinical trials required for approval of our product candidates, the regulatory submission and approval process and, even if we receive regulatory approval, the commercial launch of our products.

In addition to our current CMOs, we may rely on additional third parties to manufacture ingredients of our product candidates in the future and to perform quality testing, and reliance on these third parties entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- reduced control for certain aspects of manufacturing activities;

- termination or nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider.

We currently rely exclusively upon a single third-party manufacturer to provide NSR-REP1. Each of our other product candidates are also manufactured by a single third-party manufacturer. We do not currently have any arrangements in place for a second source for any of our product candidates or for a redundant supply. Some of our products are manufactured on a purchase order basis without a contractual commitment. In such cases, prices for manufacturing activities may vary substantially over time and adversely affect our financial results. Furthermore, we and our contract manufacturers currently rely and may in the future rely upon sole-source suppliers of certain raw materials and other specialized components of production used in the manufacture of our product candidates. For the foreseeable future, we expect to continue to rely on third-party manufacturers for any manufacturing needs for our research and development programs or our commercial supply. Should any of our product candidates receive marketing authorization, it is possible that we will only have a single manufacturer available for such product candidates for our commercial launch.

If any of our third-party manufacturers fail to fulfill our purchase orders, or if any of these manufacturers should become unavailable to us for any reason, including as a result of capacity constraints, differing priorities, financial difficulties or insolvency, we believe that there are a limited number of potential replacement manufacturers, and we likely would incur added costs and delays in identifying or qualifying such replacements. We may be unable to establish agreements with such replacement manufacturers or to do so on terms acceptable to us.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval or impact our ability to successfully commercialize any of our product candidates. Some of these events could be the basis for FDA, EMA or other regulatory authority action, including injunction, recall, seizure or total or partial suspension of product manufacture or the requirement that we repeat certain of our clinical trials.

To the extent we rely on a third-party manufacturing facility for commercial supply, that third party will be subject to significant regulatory oversight with respect to manufacturing our product candidates.

The preparation of therapeutics for clinical trials or commercial sale is subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials must be manufactured in accordance with cGMP requirements. These regulations govern manufacturing processes and procedures, including record keeping, and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of outside agents or other contaminants, or to inadvertent changes in the properties or stability of a product candidate that may not be detectable in final product testing. We must supply all necessary documentation in support of a BLA or MAA on a timely basis and must adhere to the FDA's and EMA's cGMP requirements which are enforced, in the case of the FDA, through its facilities inspection program. To the extent that we utilize third-party facilities for commercial supply, the third party's facilities and quality systems must pass an inspection for compliance with the applicable regulations as a condition of regulatory approval. In addition, the regulatory authorities may, at any time, audit or inspect the third-party manufacturing facility or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a plant inspection, the FDA or EMA may delay or not grant marketing approval.

Regulatory authorities may also audit or inspect manufacturing facilities at any time following the approval of a product for sale. If any such post-approval inspection or audit identifies a failure to comply with applicable regulations, or if a violation of product specifications or applicable regulations occurs independent of such an inspection or audit, the relevant regulatory authority may require remedial measures that may be costly or time-consuming to implement and that may include the temporary or permanent suspension of commercial sales or the temporary or permanent closure of a manufacturing facility. Any such remedial measures imposed upon our third-party manufacturers or us could harm our business, financial condition, results of operations and prospects.

We do not directly control the manufacturing of, and are completely dependent on, our CMOs for compliance with cGMP requirements. If our CMOs cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA, EMA or other regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no direct control over the ability of our CMOs to maintain adequate quality control, quality assurance and qualified personnel. Furthermore, all of our CMOs are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our CMOs to regulatory risks for the production of such materials and products. As a result, failure to meet the regulatory requirements for the production of those materials and products may generally affect the regulatory clearance of our CMOs' facilities. Our failure, or the failure of third parties, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products and product candidates.

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

Risks Related to Commercialization of Our Product Candidates

We currently have no marketing and sales force. If we are unable to establish effective sales and marketing capabilities or enter into agreements with third parties to market and sell NSR-REP1 or other product candidates that may be approved, we may not be successful in commercializing our product candidates if and when approved, and we may be unable to generate any product revenue.

If our STAR Phase 3 registrational trial is successful and NSR-REP1 is approved for commercialization, we currently intend to commercialize NSR-REP1 in the United States and Europe directly with a small specialized sales force given the orphan indication. However, we currently do not have an established marketing or sales team for the marketing, sales and distribution of any of our product candidates. In order to commercialize NSR-REP1, if approved, or any of our other product candidates that may be approved, we must build and maintain, on a territory-by-territory basis, marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our product candidates on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any product that we may develop;
- the complexity and the high degree of skill needed to administer our product candidates and our ability to recruit and train a sufficient number of surgeons to support commercialization;
- the lack of complementary treatments to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability to us from these revenue streams is likely to be lower than if we were to market, sell and distribute any product candidates that we develop ourselves. In addition, we may not be successful in entering into

arrangements with third parties to sell, market or distribute our product candidates or may be unable to do so on terms that are favorable to us. Such third parties may have interests that differ from ours. We likely will have little control over such third parties and any of them may fail to devote the necessary resources and attention to sell, market, and distribute our product candidates effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we may not be successful in commercializing our product candidates.

We also will need to train retinal surgeons to perform the procedure necessary to administer NSR-REP1 and NSR-RPGR to patients safely and effectively using our two-step process, which requires significant skill and training. Our other products may also require surgical or other complicated delivery methods. If we are unable to recruit or train sufficient retinal surgeons to perform the procedure or other delivery methods properly, the availability of NSR-REP1, NSR-RPGR or any other product could be substantially diminished.

Our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources given the low incidence and prevalence of inherited retinal diseases and may never be successful. Such efforts may require more resources than are typically required due to the complexity and uniqueness of our product candidates and the indications we are targeting. Even if our product candidates are approved, if we are unable to successfully market our products, we will not be able to generate significant revenues from such products.

We face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully market or commercialize our product candidates.

The biotechnology and pharmaceutical industries, including the gene therapy field, are characterized by rapidly changing technologies, significant competition and a strong emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, government agencies and public and private research institutions.

New developments, including the development of other pharmaceutical technologies and methods of treating disease, occur in the pharmaceutical and life sciences industries at a rapid pace. Developments by competitors may render our product candidates obsolete or noncompetitive. We anticipate that we will face intense and increasing competition as new treatments enter the market and advanced technologies become available.

We are aware of a number of companies focused on developing gene therapies in various indications, including Abeona Therapeutics Inc., Adverum Biotechnologies Inc., Allergan plc, Applied Genetic Technologies Corporation (AGTC), Audentes Therapeutics, Inc., AveXis, Inc., Biogen Inc., bluebird bio, Inc., Dimension Therapeutics, Inc., Editas Medicine, Inc., 4D Molecular Therapeutics, GenSight Biologics S.A., Homology Medicines, Inc., Horama, S.A., Limelight Bio, Inc., MeiraGTx Limited, Ophthotech Corporation, Oxford Biomedica plc, REGENXBIO Inc., Roche Holding AG, Sanofi S.A., Shire plc, Spark Therapeutics Inc. and uniQure N.V., as well as several companies addressing other methods for modifying genes and regulating gene expression. Any advances in gene therapy technology made by a competitor may be used to develop therapies that could compete against any of our product candidates.

For our specific retinal gene therapy product candidates, the main competitors in clinical development include:

- **Choroideremia:** Spark Therapeutics is currently conducting its first Phase 1/2 clinical trial of SPK-CHM, an AAV-based gene therapy for the treatment of CHM. 4D Molecular Therapeutics LLC and Biogen also have preclinical programs in CHM and we believe they may be planning to initiate clinical trials in this indication in the next 12 months.
- **X-linked Retinitis Pigmentosa:** MeiraGTx and AGTC are developing AAV-based gene therapies for the treatment of XLRP and we believe REGENXBIO and other companies may be planning to initiate clinical trials in the future. AGTC and Biogen have published both a stable mutant and a codon-optimized gene capable of producing functional RPGR.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any product candidate that we may develop. Competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly or earlier than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

In addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and/or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any product candidate that we may develop and commercialize.

The market opportunities for our product candidates may be smaller than we anticipate.

We focus our research and development efforts on treatments for rare, inherited retinal diseases. Our understanding of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, is based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. The number of patients in the United States, the European Union and elsewhere may turn out to be lower than expected or may not be otherwise amenable to treatment with our product candidates or patients may become increasingly difficult to identify and access, any of which would adversely affect our business, financial condition, results of operations and prospects.

Further, there are several factors that could contribute to making the actual number of patients who receive our potential products, if and when approved, less than the potentially addressable market. These include diagnosis and treatment criteria on such potential products' labels and the lack of widespread availability of, and limited reimbursement for, new therapies in many underdeveloped markets. Further, the severity of the progression of a disease up to the time of treatment, especially in certain inherited retinal degenerative conditions, will likely diminish the therapeutic benefit conferred by a gene therapy due to irreversible cell death. Lastly, certain patients' immune systems might reduce efficacy or prohibit the successful delivery of certain gene therapy products to the target tissue, thereby limiting the treatment outcomes.

Ethical, legal and social issues related to genetic testing may reduce demand for any gene therapy products for which we obtain marketing approval.

We anticipate that prior to receiving certain gene therapies, patients would be required to undergo genetic testing. Genetic testing has raised concerns regarding the appropriate utilization and the confidentiality of information provided by genetic testing. Genetic tests for assessing a person's likelihood of developing a chronic disease have focused public attention on the need to protect the privacy of genetic information. For example, concerns have been expressed that insurance carriers and employers may use these tests to discriminate on the basis of genetic information, resulting in barriers to the acceptance of genetic tests by consumers. This could lead to governmental authorities restricting genetic testing or calling for limits on or regulating the use of genetic testing, particularly for diseases for which there is no known cure. Any of these scenarios could decrease demand for any gene therapy products for which we obtain marketing approval.

The commercial success of our product candidates will depend upon its degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

Even with the requisite approvals from the FDA, EMA and other regulatory authorities internationally, the commercial success of our product candidates will depend, in part, on the acceptance of physicians, patients and third-party payors of gene therapy products in general, and our product candidates in particular, as medically

necessary, cost-effective and safe. Any product that we commercialize may not gain acceptance by physicians, patients, third-party payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of gene therapy products and, in particular, our product candidates, if approved for commercial sale, will depend on several factors, including:

- the efficacy and safety of our product candidates as demonstrated in clinical trials and in the market;
- the potential and perceived advantages of our product candidates over alternative treatments;
- the availability and cost of treatment relative to alternative treatments;
- patient awareness of, and willingness to seek, genotyping;
- the willingness of physicians to prescribe, and the target patient population to try, new therapies;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of the FDA, EMA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling;
- relative convenience and ease of administration;
- patient willingness to undergo a surgical procedure;
- the timing of market introduction of competitive products;
- the strength of marketing and distribution support;
- publicity concerning our product candidates or competing products and treatments; and
- favorable third-party payor coverage and adequate reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product will not be fully known until after it is launched.

Specifically, our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe. Gene therapy may not gain the acceptance of the public or the medical community. Our success will in part depend upon physicians who specialize in the treatment of genetic diseases targeted by our product candidates, prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments with which they are familiar and for which greater clinical data may be available.

The insurance coverage and reimbursement status of newly approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate product revenue.

We expect the cost of a single administration of gene therapy products, such as those we are developing, to be substantial, when and if they achieve regulatory approval. We expect that coverage and adequate reimbursement by government and private payors will be essential for most patients to be able to afford these treatments. Accordingly, sales of any product candidates for which we obtain marketing approval will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other third-party payors. Coverage and reimbursement by a third-party payor may depend upon several factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient and the indication;

- convenient and easy-to-administer compared to alternative treatments;
- cost-effective compared to alternative treatments; and
- neither experimental nor investigational.

Obtaining coverage and reimbursement for a product from third-party payors is a time-consuming and costly process that could require us to provide to the payor supporting scientific, clinical and cost-effectiveness data. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If coverage and reimbursement are not available, or are available only at 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 adequate to realize a sufficient return on our investment. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. 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. Assuming we obtain coverage for a given product by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third-party payors to reimburse all or part of the costs associated with their prescription drugs. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover all or a significant portion of the cost of our products. Therefore, coverage and adequate reimbursement is critical to new product acceptance. Additionally, there may be significant delays in obtaining coverage and reimbursement for newly approved drugs and biologics, and coverage may be more limited than the purposes for which the drug is approved by the FDA or comparable foreign regulatory authorities.

There is significant uncertainty related to third-party coverage and reimbursement of newly approved products, including potential one-time gene therapies. In the United States, third-party payors, including government payors such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered and reimbursed. The Medicare and Medicaid programs increasingly are used as models for how private payors develop their coverage and reimbursement policies. However, no uniform policy of coverage and reimbursement exists among third-party payors. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. One payor's determination to provide coverage for a product does not assure that other payors will also provide coverage, and adequate reimbursement. Increasingly, third-party payors are also requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Currently, only one gene therapy product has been approved for coverage and reimbursement by the Centers for Medicare and Medicaid Services, or CMS, the agency responsible for administering the Medicare program. It is difficult to predict what the CMS will decide with respect to coverage and reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these types of products. Moreover, reimbursement agencies in the European Union or elsewhere may be more conservative than the CMS. For example, several cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European Union Member States. It is difficult to predict what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures, and foreign governments have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. For example, in the United States, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the PPACA, contains provisions that may reduce the profitability of products, including, for example, increased rebates for products sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs.

Further, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, contain the cost of drugs, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, the Trump Administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require authorization through additional legislation to become effective, Congress and the Trump Administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Outside the United States, international operations generally are subject to extensive government price controls and other market regulations, and increasing emphasis on cost-containment initiatives in the European Union, Canada and other countries may put pricing pressure on us. For example, two gene therapy products have been approved in the European Union; one has since been withdrawn from the market and its approval has expired, and the other has yet to be widely available commercially. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medical products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our product candidates may be reduced compared with the United States and may be insufficient to generate commercially reasonable product revenues.

Additionally, in countries where the pricing of gene therapy products is subject to governmental control, pricing negotiations with governmental authorities can take considerable time after the 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 European Union Member States and parallel distribution, or arbitrage between low-priced and high-priced Member States, can further reduce prices. To obtain reimbursement or pricing approval in some countries, we may be required to conduct one or more studies that compare the cost-effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed.

Moreover, increasing efforts by government and third-party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. Payors increasingly are considering new metrics as the basis for reimbursement rates, such as average sales price, average manufacturer price and actual acquisition cost. The existing data for reimbursement based on some of these metrics is relatively limited, although certain states have begun to survey acquisition cost data for the purpose of setting Medicaid reimbursement rates, and CMS has begun making pharmacy National Average Drug Acquisition Cost and National Average Retail Price data publicly available on at least a monthly basis. The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug and device 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 foreign 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 our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate

from the sale of the product in that country. To obtain reimbursement or pricing approval in some countries, we may be required to conduct one or more studies that compare the cost-effectiveness of our product candidate to other available therapies. 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.

In the European Union, for example, each European Union Member State may determine those products for which its national health insurance system provides reimbursement and may control the prices of medicinal products for human use marketed in its territory. As a result, following receipt of marketing authorization in the European Union, through any application route, a marketing authorization holder would usually engage in pricing discussions and negotiations with the competent pricing authority in the individual European Union Member States. Some European Union Member States operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed upon. Others approve a specific price for the medicinal product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. The downward pressure on healthcare costs in general, particularly prescription drugs, has become more intense and continues on that trajectory. As a result, increasingly high barriers are being erected to the entry of new products. In addition, we may face competition for our product candidates from lower priced products in foreign countries that have placed price controls on pharmaceutical products.

A health technology assessment, or HTA, of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in European Union Member States. An HTA is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. An HTA generally focuses on the clinical efficacy, safety, cost, and cost-effectiveness of individual medicinal products as well as their potential implications for the healthcare system. Those elements of medicinal products are compared with other treatment options available on the market. The outcome of an HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual European Union Member States. In some Member States (such as the United Kingdom or Ireland), the outcome of an HTA is a critical factor to a product's reimbursement status. The extent to which pricing and reimbursement decisions are influenced by the HTA of the specific medicinal product varies between European Union Member States. In addition, pursuant to Directive 2011/24/EU on the application of patients' rights in cross-border healthcare, a voluntary network of national authorities or bodies responsible for an HTA in the individual European Union Member States was established. The purpose of the network is to facilitate and support the exchange of scientific information concerning HTAs. This may lead to European Union Member States taking a more harmonized approach to HTAs and consequently in how they approach pricing and reimbursement decisions and may negatively affect pricing of certain products in at least some European Union Member States. On January 31, 2018, the European Commission adopted a proposal for a regulation on HTAs. This legislative proposal intends to boost cooperation amongst European Union Member States for assessing health technologies. If adopted in its current form, the regulation will permit and equip European Union Member States to use common HTA tools, methodologies and procedures.

Therefore, it may be difficult to project the impact of these evolving reimbursement metrics on the willingness of payors to cover product candidates that we or our partners are able to commercialize. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products such as ours.

Risks Related to Our Intellectual Property

Our rights to develop and commercialize our product candidates are subject to the terms and conditions of licenses granted to us by others.

We do not currently own any issued patents and we are heavily reliant upon licenses from Oxford University Innovation Limited (formerly, Isis Innovation Limited), or Oxford, to certain patent rights and proprietary technology that are important or necessary to the development of our technology and product candidates, including

the patents and know-how relating to vectors for use in gene therapy for CHM. These and other licenses may not provide exclusive rights to use such intellectual property and technology or may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and product candidates in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products, including in territories covered by our licenses. These licenses may also require us to grant back certain rights to licensors and to pay certain amounts relating to sublicensing patent and other rights under the agreement.

In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain, enforce, or defend the patents, covering technology that we license from third parties. For example, Oxford retains control of such activities. Therefore, we cannot be certain that the Oxford patents and patent applications will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If our licensors fail to maintain such patents or patent applications, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our product candidates that are the subject of such licensed rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties will also apply to patent rights we may own in the future.

Licenses to additional third-party technology and materials that may be required for our development programs, including additional technology and materials owned by any of our current licensors, may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have an adverse effect on our business, financial condition, results of operations and prospects.

If we are unable to obtain and maintain patent protection for our current product candidates, any future product candidates we may develop and our technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize our products and technology may be adversely affected.

Our success depends, in large part, on our ability to seek, obtain and maintain patent protection in the United States and other countries with respect to our product candidates and to future innovation related to our manufacturing technology. Our licensors have sought and we intend to seek to protect our proprietary position by filing patent applications in the United States, the United Kingdom and elsewhere, related to certain technologies and our product candidates that are important to our business. Our current patent portfolio contains a limited number of granted and issued patents and patent applications, the majority of which are in-licensed from third parties and relate to compositions related to gene therapy vectors and methods of use of those vectors. However, the risks associated with patent rights generally apply to patent rights that we in-license now or in the future, as well as patent rights that we may own in the future. Moreover, the risks apply with respect to patent rights and other intellectual property applicable to our product candidates, as well as to any intellectual property rights that we may acquire in the future related to future product candidates, if any.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, enforce, defend or license all necessary or desirable patent applications at a reasonable cost or in a timely manner.

In some cases, the work of certain academic researchers in the gene therapy field has entered the public domain, which we believe precludes our ability to obtain patent protection for certain inventions relating to such work. Consequently, we will not be able to assert any such patents to prevent others from using our technology for, and developing and marketing competing products to treat, these indications. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

We are a party to intellectual property license agreements with Oxford and Oxford BioMedica (UK) Limited, or BioMedica, which are important to our business, and we expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various due diligence, development and commercialization timelines, milestone payments, royalties and other obligations on us. See the description in the section titled “Item 4.B. Information on the Company—Business Overview—Collaborations and License Agreements” in our Annual Report on Form 20-F for the fiscal year ended December 31, 2017.

If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, or, in some cases, under other circumstances, the licensor may have the right to terminate the license, in which event we would not be able to market product candidates covered by the license. In addition, certain of these license agreements are not assignable by us without the consent of the respective licensor, which may have an adverse effect on our ability to engage in certain transactions.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has, in recent years, been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of any patent rights are highly uncertain. Our licensed patent applications may not result in patents being issued which protect our technology or product candidates, effectively prevent others from commercializing competitive technologies and product candidates or otherwise provide any competitive advantage. In fact, patent applications may not issue as patents at all. During prosecution of any patent application, the issuance of any patents based on the application may depend upon our ability to generate additional preclinical or clinical data that support the patentability of our proposed claims. We may not be able to generate sufficient additional data on a timely basis, or at all. Even assuming patents issue from patent applications in which we have rights, changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our or our licensors' patent protection.

Other parties have developed technologies that may be related or competitive to our own and such parties may have filed or may file patent applications, or may have received or may receive patents, claiming inventions that may overlap or conflict with those claimed in our own patent applications or issued patents. We may not be aware of all third-party intellectual property rights potentially relating to our current and future product candidates. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and in other jurisdictions are typically not published until 18 months after filing, or, in some cases, not at all. Therefore, we cannot know with certainty whether the inventors of our licensed patents and applications were the first to make the inventions claimed in those patents or pending patent applications, or that they were the first to file for patent protection of such inventions. Similarly, should we own any patents or patent applications in the future, we may not be certain that we were the first to file for patent protection for the inventions claimed in such patents or patent applications. Even if the patent applications we license or may own in the future do issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. As a result, the issuance, scope, validity and commercial value of our patent rights cannot be predicted with any certainty.

The degree of patent protection we require to successfully compete in the marketplace may be unavailable or severely limited in some cases and may not adequately protect our rights or permit us to gain or keep any competitive advantage. We cannot provide any assurances that any of our licensed patents have, or that any of our pending licensed patent applications that mature into issued patents will include, claims with a scope sufficient to protect our product candidates or otherwise provide any competitive advantage. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our licensed patent portfolio may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our product candidates, including biosimilar versions of such products. In addition, the intellectual property portfolio licensed to us by Oxford may be used by them or licensed to third parties, and such third parties may have certain enforcement rights. Thus, patents licensed to us could be put at risk of being invalidated or interpreted narrowly in litigation filed by or against our licensors or another licensee or in administrative proceedings brought by or against our licensors or another licensee in response to such litigation or for other reasons.

Even if we acquire patent protection that we expect should enable us to maintain some competitive advantage, third parties, including competitors, may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. In litigation, a competitor could claim that our patents, if issued, are not valid for a number of reasons. If a court agrees, we would lose our rights to those challenged patents.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability and our licensed patents may be challenged in courts or patent offices in the United States and abroad. For example, we may be subject to a third-party submission of prior art to the U.S. Patent and Trademark Office, or USPTO, challenging the validity of one or more claims of our licensed patents. Such submissions may also be made prior to a patent's issuance, precluding the granting of a patent based on one of our pending licensed patent applications. We may become involved in opposition, derivation, reexamination, *inter partes* review, post-grant review or interference proceedings challenging the patent rights of others from whom we have obtained licenses to such rights. Competitors may claim that they invented the inventions claimed in our licensed issued patents or patent applications prior to the inventors of such patents or applications, or may have filed patent applications before Oxford or BioMedica, as owner of the patent rights. A competitor who can establish an earlier filing or invention date may also claim that we are infringing their patents and that we therefore cannot practice our technology as claimed under our licensed patents, if issued. Competitors may also contest our licensed patents, if issued, by showing that the invention was not patent-eligible, was not novel, was obvious or that the patent claims failed any other requirement for patentability.

In addition, Oxford may in the future be subject to claims by former employees or consultants asserting an ownership right in our licensed patent applications, as a result of the work they performed. An adverse determination in any such submission or proceeding may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar technology and therapeutics, without payment to us, or could limit the duration of the patent protection covering our technology and product candidates. Such challenges may also result in our inability to manufacture or commercialize our product candidates without infringing third-party patent rights. 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 they are unchallenged, our licensed patents and pending patent applications, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims to circumvent our licensed patents by developing similar or alternative technologies or therapeutics in a non-infringing manner. For example, a third party may develop a competitive therapeutic that provides benefits similar to one or more of our product candidates but that uses a vector or an expression construct that falls outside the scope of our patent protection. If the patent protection provided by the patents and patent applications we hold or pursue with respect to our product candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our product candidates could be negatively affected, which would harm our business.

Our intellectual property licenses with third parties may be subject to disagreements over contract interpretation, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors.

We currently depend, and will continue to depend, on our license agreements, including our agreements with Oxford and BioMedica, whereby we obtain rights in certain patents and patent applications owned by them. Further development and commercialization of our current product candidates may, and development of any future product candidates will, require us to enter into additional license or collaboration agreements, including, potentially, additional agreements with Oxford or BioMedica. The agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, result in loss of access, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have an adverse effect on our business, financial condition, results of operations and prospects.

If any of our licenses or material relationships or any in-licenses upon which our licenses are based are terminated or breached, we may:

- lose our rights to develop and market our product candidates;

- lose patent protection for our product candidates;
- experience significant delays in the development or commercialization of our product candidates;
- not be able to obtain any other licenses on acceptable terms, if at all; or
- incur liability for damages.

In addition, a third party may in the future bring claims that our performance under our license agreements, including our sponsoring of clinical trials, interferes with such third party's rights under its agreement with one of our licensors. If any such claim were successful, it may adversely affect our rights and ability to advance our product candidates as a clinical candidates or subject us to liability for monetary damages, any of which would have an adverse effect on our business, financial condition, results of operations and prospects.

These risks apply to any agreements that we may enter into in the future for our current or any future product candidates. If we experience any of the foregoing, it could have a negative impact on our business, financial condition, results or operations and prospects.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We have entered into license agreements with third parties and may need to obtain additional licenses from one or more of these same third parties or from others to advance our research or allow commercialization of our product candidates. It is possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize our product candidates, which could harm our business. We cannot provide any assurances that third-party patents or other intellectual property rights do not exist which might be enforced against our current or future manufacturing methods or product candidates, resulting in either an injunction prohibiting our manufacture or sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties.

In each of our existing license agreements, and we expect in our future agreements, patent prosecution of our licensed technology is controlled solely by the licensor, and we may be required to reimburse the licensor for their costs of patent prosecution. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using the intellectual property. Our license agreements with Oxford also require us to meet development thresholds to maintain each license, including establishing a set timeline for developing and commercializing product candidates. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights pursuant to our collaborative development relationships;
- our diligence obligations under the license agreements and what activities satisfy those diligence obligations;
- the inventorship or ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize our product candidates.

We may not be successful in obtaining necessary rights to our product candidates through acquisitions and in-licenses.

We currently have certain rights to the intellectual property, through licenses from third parties, to develop our product candidates. Because our programs may require the use of additional proprietary rights held by these or other third parties, the growth of our business likely will depend, in part, on our ability to acquire, in-license or use these proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes or other intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive. 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.

We may collaborate with non-profit and academic institutions to accelerate our preclinical research and development under written agreements with these institutions. These institutions may provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property or maintain the existing intellectual property rights we have, we may have to abandon development of our product candidates and our business, financial condition, results of operations and prospects could suffer. Moreover, to the extent that we seek to develop other product candidates in the future, we will likely require acquisition or in-license of additional proprietary rights held by third parties.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by government patent agencies, and our patent protection could be reduced or eliminated as a result of non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our licensed patents and/or applications and any patent rights we may own in the future. We rely on our outside counsel or our licensing partners to pay these fees due to non-U.S. patent agencies. The USPTO and various non-U.S. government patent agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply and we are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market and this circumstance could have an adverse effect on our business.

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

Filing, prosecuting 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 could be less extensive than those in the United States. In some cases, we may not be able to obtain patent protection for certain licensed technology outside the United States. Even if we obtain licenses granting us worldwide rights, patents or

patent applications might not have been pursued in each jurisdiction. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States, even in jurisdictions where we do pursue patent protection. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, even in jurisdictions where we do pursue patent protection, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not pursued and 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 our 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 foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products or methods of treatment, which could make it difficult for us to stop the infringement of our patents, if pursued and obtained, or marketing of competing products in violation of our proprietary rights generally. For example, an April 2018 report from the Office of the United States Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. Proceedings to enforce our patent rights in foreign 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 and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court. We may not be able to protect our trade secrets in court.

If one of our licensing partners or we initiate legal proceedings against a third party to enforce a patent covering our product candidates, assuming such a patent has issued or does issue, the defendant could counterclaim that the patent covering our product candidates is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could include an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, lack of written description, non-enablement or failure to claim patent-eligible subject matter. Grounds for an unenforceability assertion could include an allegation that someone connected with prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution.

Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include pre-issuance submissions, *ex parte* re-examination, post-grant review, *inter partes* review and equivalent proceedings in foreign jurisdictions. Some of these mechanisms may even be exploited anonymously by third parties. Such proceedings could result in the revocation or cancellation of or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensing partners were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection could have an adverse impact on our business.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, collaborators, scientific advisors and contractors. However, we may

not be able to prevent the unauthorized disclosure or use of our technical know-how or other trade secrets by the parties to these agreements, despite the existence generally of confidentiality agreements and other contractual restrictions. Monitoring unauthorized uses and disclosures is difficult and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of the collaborators, scientific advisors, employees and consultants who are parties to these agreements breach or violate the terms of any of these agreements, we may not have adequate remedies for any such breach or violation. As a result, we could lose our trade secrets.

We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements and security measures, they may still be breached, and we may not have adequate remedies for any breach.

In addition, our trade secrets may otherwise become known or be independently discovered by competitors. Competitors could purchase our product candidates and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate such trade secrets, from using that technology or information to compete with us. If our trade secrets are not adequately protected so as to protect our market against competitors' therapeutics, our competitive position could be adversely affected, as could our business.

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

Our commercial success depends upon our ability and the ability of our future collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may in the future become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technology, including interference proceedings, *ex parte* re-examination, post-grant review and *inter partes* review before the USPTO. Our competitors or other third parties may assert infringement claims against us, alleging that our products, manufacturing methods, formulations or administration methods are covered by their patents. Given the vast number of patents in our field of technology, we cannot be certain or guarantee that we do not infringe existing patents or that we will not infringe patents that may be granted in the future. Many companies and institutions have filed, and continue to file, patent applications related to gene therapy and related manufacturing methods. Some of these patent applications have already been allowed or issued and others may issue in the future. For example, we are aware of an issued U.S. patent and an allowed U.S. patent application and foreign counterparts thereof that claim codon-optimized versions of the RPGR gene. Since this area is competitive and of strong interest to pharmaceutical and biotechnology companies, there will likely be additional patent applications filed and additional patents granted in the future, as well as additional research and development programs expected in the future. Furthermore, because patent applications can take many years to issue, may be confidential for 18 months or more after filing and can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use, sale or importation of our product candidates and we may or may not be aware of such patents. If a patent holder believes the manufacture, use, sale or importation of one of our product candidates infringes its patent, the patent holder may sue us even if we have licensed other patent protection for our technology. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant product revenue and against whom our licensed patent portfolio may therefore have no deterrent effect.

It is also possible that we have failed to identify relevant third-party patents or applications. For example, applications filed before November 29, 2000 and certain applications filed after that date that will not be filed outside the United States may remain confidential until patents issue. Moreover, it is difficult for industry

participants, including us, to identify all third-party patent rights that may be relevant to our product candidates and technologies because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. We may fail to identify relevant patents or patent applications or may identify pending patent applications of potential interest but incorrectly predict the likelihood that such patent applications may issue with claims of relevance to our technology. In addition, we may be unaware of one or more issued patents that would be infringed by the manufacture, sale or use of a current or future product candidate, or we may incorrectly conclude that a third-party patent is invalid, unenforceable or not infringed by our activities. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our technologies, our product candidates or the use of our product candidates.

Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent or other intellectual property rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could adversely affect our ability to commercialize our product candidates. 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. Similarly, there is no assurance that a court of competent jurisdiction would find that product candidates or our technology did not infringe a third-party patent.

If we are found, or believe there is a risk that we may be found, to infringe a third party's valid and enforceable intellectual property rights, we could be required or may choose to obtain a license from such third party to continue developing, manufacturing and marketing our product candidates and technology. However, we may not be able to obtain any required license 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. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product candidate. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from manufacturing and commercializing our product candidates or force us to cease some or all of our business operations, which could harm our business. In addition, we may be forced to redesign our product candidates, seek new regulatory approvals and indemnify third parties pursuant to contractual agreements. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, reputation, financial condition, results of operations and prospects.

Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.

Litigation or other legal proceedings relating to intellectual property claims, with or without merit, are unpredictable and generally expensive and time-consuming. Competitors may infringe our intellectual property rights or the intellectual property rights of our licensing partners, or we may be required to defend against claims of infringement. To counter infringement or unauthorized use claims or to defend against claims of infringement can be expensive and time consuming. Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. 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, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our ADSs. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities.

We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios.

Accordingly, despite our efforts, we may not be able to prevent third parties from infringing, misappropriating or successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a negative impact on our ability to compete in the marketplace.

We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Many of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors, as well as our academic partners. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights and adversely effect our reputation. An inability to incorporate such technologies or features would harm our business and may prevent us from successfully commercializing our product candidates. In addition, we may lose personnel as a result of such claims and any such litigation or the threat thereof may adversely affect our ability to hire employees or contract with independent contractors. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our product candidates, which would have an adverse effect on our business, results of operations and financial condition. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to 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. Moreover, even when we obtain agreements assigning intellectual property to us, 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. Furthermore, individuals executing agreements with us may have preexisting or competing obligations to a third party, such as an academic institution, and thus an agreement with us may be ineffective in perfecting ownership of inventions developed by that individual. Disputes about the ownership of intellectual property that we may own may have an adverse effect on our business.

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

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes several significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted and also may affect patent litigation. These also include provisions that switched the United States from a "first-to-invent" system to a "first-to-file" system, allow third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent through various post-grant proceedings administered by the USPTO. Under a first-to-file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO has promulgated new 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-to-file provisions, only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could 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 have a negative impact effect on our business, financial condition, results of operations and prospects.

As an example, the Leahy-Smith Act provides a new administrative tribunal known as the Patent Trial and Appeals Board, or PTAB, that provides a venue for companies to challenge the validity of competitor patents at a cost that is much lower than district court litigation and on timelines that are much faster. Although it is not clear what, if any, long-term impacts the PTAB proceedings will have on the operation of our business, the initial results of patent challenge proceedings before the PTAB since its inception in 2013 have resulted in the invalidation of many U.S. patent claims. The availability of the PTAB as a lower-cost, faster and potentially more potent tribunal for challenging patents could therefore increase the likelihood that our own licensed patents will be challenged, thereby increasing the uncertainties and costs of maintaining and enforcing them.

We also may be subject to a third-party pre-issuance submission of prior art to the USPTO, or become involved in other contested proceedings such as opposition, derivation, reexamination, *inter partes* review, or post-grant review proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. 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 products.

The patent positions of companies engaged in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Two cases involving diagnostic method claims and "gene patents" have been decided by the Supreme Court of the United States, or the Supreme Court. On March 20, 2012, the Supreme Court issued a decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, or *Prometheus*, a case involving patent claims directed to a process of measuring a metabolic product in a patient to optimize a drug dosage for the patient. According to the Supreme Court, the addition of well-understood, routine or conventional activity such as "administering" or "determining" steps was not enough to transform an otherwise patent-ineligible natural phenomenon into patent-eligible subject matter. On July 3, 2012, the USPTO issued a guidance memo to patent examiners indicating that process claims directed to a law of nature, a natural phenomenon or a naturally occurring relation or correlation that do not include additional elements or steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to patent-ineligible subject matter. On June 13, 2013, the Supreme Court issued its decision in Association for *Molecular Pathology v. Myriad Genetics, Inc.*, or *Myriad*, a case involving patent claims held by Myriad Genetics, Inc. relating to the breast cancer susceptibility genes BRCA1 and BRCA2. In *Myriad*, the Supreme Court held that an isolated segment of naturally occurring DNA, such as the DNA constituting the BRCA1 and BRCA2 genes, is not patent-eligible subject matter, but that complementary DNA, which is an artificial construct that may be created from RNA transcripts of genes, may be patent-eligible.

On March 4, 2014, the USPTO issued a guidance memorandum to patent examiners titled, "2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena, and/or Natural Products." On December 6, 2014, a memorandum entitled "2014 Interim Guidance on Subject Matter Eligibility" was published. On July 30, 2015, an update pertaining to patent subject matter eligibility was published by the USPTO. These guidelines instruct USPTO examiners on the ramifications of the *Prometheus* and *Myriad* rulings and apply the *Myriad* ruling to natural products and principles including all naturally occurring nucleic acids. Certain of our licensed patents and patent applications contain claims that relate to specific DNA sequences that are naturally occurring at least in part and, therefore, could be the subject of future challenges made by third parties. In addition, the recent USPTO guidance could impact our ability to pursue similar patent claims in patent applications we may prosecute in the future.

We cannot assure you that our efforts to seek patent protection for our technology and product candidates will not be negatively impacted by the decisions described above, rulings in other cases or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact the Supreme Court's decisions in *Prometheus* and *Myriad* may have on the ability of life science companies to obtain or enforce patents relating to their products and technologies in the future. These decisions, the guidance issued by the USPTO and rulings in other cases or changes in USPTO guidance or procedures could have a negative impact on our existing patent portfolio and our ability to protect and enforce our intellectual property in the future.

Moreover, although the Supreme Court has held in *Myriad* that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene-related patent claims, and we may deem it necessary to defend ourselves against these claims by asserting non-infringement and/or invalidity positions, or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be subjected to an injunction that would prevent us from utilizing the patented subject matter. Such outcomes could harm our business, financial condition, results of operations or prospects.

Outside the United States, other courts have also begun to address the patenting of genetic material. In August 2015, the Australian High Court ruled that isolated genes cannot be patented in Australia. The decision did not address methods of using genetic material. Any ruling of a similar scope in other countries could affect the scope of our intellectual property rights.

If we do not obtain patent term extensions and data exclusivity for our product candidates, our business may be harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of our product candidates, one or more U.S. patents that we license or may own in the future may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent 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. Further, certain of our licenses currently or in the future may not provide us with the right to control patent-term extension decisions under the Hatch-Waxman Amendments. Thus, if one of our important licensed patents is eligible for a patent term extension under the Hatch-Waxman Amendments, and it covers a product of another licensee in addition to our own product candidate, we may not be able to obtain an extension if the other licensee seeks and obtains that extension first. We also may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. In addition, to the extent we wish to pursue patent term extension based on a patent that we in-license from a third party, we would need the cooperation of that third party. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may be able to enter the market sooner, and our revenue could be reduced.

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

We do not currently have any registered trademarks and we have not filed any trademark applications to date. Any trademark applications in the United States, Europe and in other foreign jurisdictions where we may file may not be allowed or may subsequently be opposed. Once filed and registered, our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. As a means to enforce our 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, particularly for a company of our size. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our business, financial condition, results of operations, or prospects.

Intellectual property rights and regulatory exclusivity 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 gene therapy products that are similar to our product candidates but that are not covered by the claims of the patents that we license or may own in the future;
- we, or our license partners or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent applications that we license or may own in the future;
- we, or our license partners or 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 licensed intellectual property rights;
- others may circumvent our regulatory exclusivities, such as by pursuing approval of a competitive product candidate via the traditional approval pathway based on their own clinical data, rather than relying on the abbreviated pathway provided for biosimilar applicants;
- it is possible that our pending licensed patent applications or those that we may own in the future will not lead to issued patents;
- issued patents that we hold rights to now or in the future may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- others may have access to the same intellectual property rights licensed to us on a non-exclusive basis;
- 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 our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents or other intellectual property rights of others may have an adverse effect on our business; or
- we may choose not to file a patent for certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

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

Risks Related to Government Regulation

Even if we complete the necessary clinical trials, we cannot predict when, or if, we will obtain regulatory approval to commercialize our product candidates and the approval may be for a more narrow indication than we seek.

We cannot commercialize a product candidate until the appropriate regulatory authorities have reviewed and approved the product candidate. The FDA must review and approve any new pharmaceutical product before it can be marketed and sold in the United States. The FDA regulatory review and approval process, which includes evaluation of preclinical studies and clinical trials of a product candidate and proposed labeling, as well as the evaluation of the manufacturing process and manufacturers' facilities, is lengthy, expensive and uncertain. To obtain approval, we must, among other things, demonstrate with substantial evidence from well-controlled clinical trials that the product candidate is both safe and effective for each indication where approval is sought. Even if our

product candidates meet the FDA's safety and efficacy endpoints in clinical trials, the FDA may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. The FDA has substantial discretion in the review and approval process and may refuse to file our application for substantive review or may determine after review of our data that our application is insufficient to allow approval of our product candidates. The FDA may require that we conduct additional preclinical studies, clinical trials or manufacturing validation studies and submit that data before it will reconsider our application. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory authority policy during the period of product development, clinical trials and the review process.

The FDA, EMA or other regulatory authorities also may approve a product candidate for more limited indications than requested or may impose significant limitations in the form of narrow indications, warnings or a REMS. These regulatory authorities may require precautions or contraindications with respect to conditions of use or may grant approval subject to the performance of costly post-marketing clinical trials. In addition, the FDA, EMA or other regulatory authorities may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. Any of the foregoing scenarios could harm the commercial prospects for our product candidates and negatively impact our business, financial condition, results of operations and prospects.

Delays in obtaining regulatory approval of our manufacturing process and facility or disruptions in our manufacturing process may delay or disrupt our product development and commercialization efforts. To date, to our knowledge, a limited number of cGMP gene therapy manufacturing facilities in the United States have received approval from the FDA for the manufacture of an approved gene therapy product.

We do not currently operate manufacturing facilities for clinical or commercial production of our product candidates. Before we can begin to commercially manufacture our product candidates, whether in a third-party facility or in our own facility, once established, we must obtain regulatory approval from the FDA for our manufacturing process and facility. A manufacturing authorization must also be obtained from the appropriate European Union regulatory authorities. To date, to our knowledge, a limited number of cGMP gene therapy manufacturing facilities have received approval from the FDA for the manufacture of an approved gene therapy product and, therefore, the timeframe required for us to obtain such approval is uncertain. In addition, we or a third-party manufacturer must pass a pre-approval inspection of the manufacturing facility by the FDA before our product candidates can obtain marketing approval. In order to obtain approval, we will need to ensure that all of our processes, methods and equipment are compliant with cGMPs, and perform extensive audits of vendors, contract laboratories and suppliers. If any of our vendors, contract laboratories or suppliers are found to be non-compliant with cGMPs, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors. The cGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with cGMPs, we will be obligated to expend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any product candidate that we may develop.

If we or our third-party manufacturers fail to comply with applicable cGMP regulations, the FDA, EMA and other regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product candidate or suspension or revocation of a pre-existing approval. Such an occurrence may cause our business, financial condition, results of operations and prospects to be harmed.

Additionally, if the supply from our third-party manufacturers is interrupted, there could be a significant disruption in commercial supply of our products. We do not currently have a backup manufacturer of our product candidate supply for clinical trials or commercial sale. An alternative manufacturer would need to be qualified through a supplement to its regulatory filing, which could result in further delays. The regulatory authorities also may require additional clinical trials if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and could result in a delay in our desired clinical and commercial timelines.

If our competitors are able to obtain orphan drug exclusivity for products that constitute the same drug and treat the same indications as our product candidates, we may not be able to have competing products approved by applicable regulatory authorities for a significant period of time. In addition, even if we obtain orphan drug exclusivity for any of our products, such exclusivity may not protect us from competition.

Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate products for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product.

We have received orphan drug designation for NSR-REP1 for the treatment of CHM from the FDA in the United States and from the EMA in the European Union. We have also received orphan drug designation for NSR-RPGR for the treatment of XLRP from the EMA in the European Union. The designation of any of our product candidates as an orphan product does not guarantee that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval. For example, we are aware that Spark Therapeutics Inc. was also granted orphan product designation by the EMA and FDA for its product candidate for the treatment of CHM and is currently enrolling patients in a Phase 1/2 clinical trial.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or the EMA from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable orphan drug exclusivity period is seven years in the United States and ten years in the European Union. The orphan drug exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

On August 3, 2017, the Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA's pre-existing regulatory interpretation to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

- the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or
- the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

Regenerative medicine advanced therapy, or RMAT, designation for NSR-REP1 may not lead to faster development or regulatory processes nor does it increase the likelihood that NSR-REP1 will receive marketing approval for CHM.

RMAT was introduced as a new designation under the 21st Century Cures Act for the development and review of certain regenerative medicine therapies. To receive RMAT designation, a regenerative medicine product candidate must be intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition with preliminary clinical evidence indicating that the drug has the potential to address unmet medical need. RMAT designation does not require evidence to indicate that the drug may offer a substantial improvement over available therapies, as breakthrough designation requires.

An RMAT product candidate receives: intensive guidance on an efficient drug development program; intensive involvement of senior managers and experienced staff on a proactive, collaborative and cross-disciplinary review; and a rolling review. Regenerative medicine therapies that quality for RMAT designation may also quality for other FDA expedited programs, including fast track designation, breakthrough therapy designation, accelerated approval and priority review designation, if they meet the criteria for such programs. However, RMAT designation does not assure that marketing approval will be granted and, if granted, that the approval process would be any faster than it would have otherwise been.

In June 2018, we received RMAT designation for NSR-REP1 for the treatment of CHM. However, there is no guarantee that the receipt of RMAT designation will result in a faster development process, review or approval for NSR-REP1 in CHM or increase the likelihood that NSR-REP1 will be granted marketing approval for CHM. Likewise, any future RMAT designation or other expedited review status such as breakthrough therapy designation for any of our other product candidates neither guarantees a faster development process, review or approval nor improves the likelihood of the grant of marketing approval by FDA for any such product candidate compared to drugs considered for approval under conventional FDA procedures. In addition, the FDA may withdraw any RMAT or other expedited review status at any time. We may seek RMAT or breakthrough therapy designation for our other product candidates, but the FDA may not grant this status to any such product candidates.

We may seek fast track designation by the FDA for one or more of our product candidates, but we might not receive such designation, and even if we do, such designation may not actually lead to a faster development or regulatory review or approval process.

If a product is intended for the treatment of a serious or life-threatening condition and the product demonstrates the potential to address unmet needs for this condition, the treatment sponsor may apply for FDA fast track designation. If we seek fast track designation for a product candidate, we may not receive it from the FDA. However, even if we receive fast track designation, fast track designation does not ensure that we will receive marketing approval or that approval will be granted within any particular timeframe. We may not experience a faster development, regulatory review or approval process with fast track designation compared to conventional FDA procedures. Additionally, the FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program. Fast track designation alone does not guarantee qualification for the FDA's priority review procedures.

A breakthrough therapy designation by the FDA for a product candidate may not lead to a faster development or regulatory review or approval process, and it would not increase the likelihood that the product candidate will receive marketing approval.

We may seek a breakthrough therapy designation for one or more product candidates. A breakthrough therapy is defined as a product candidate that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For product candidates that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Product candidates designated as breakthrough therapies by the FDA are also eligible for priority review if supported by clinical data at the time of the submission of the NDA.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to product candidates considered for approval under conventional FDA procedures and it would not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the product candidate no longer meets the conditions for qualification or it may decide that the time period for FDA review or approval will not be shortened.

Any product candidate for which we obtain marketing approval could be subject to post-marketing restrictions or withdrawal from the market and we may be subject to substantial penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Even if we obtain regulatory approval for our product candidates, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. For example, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. FDA guidance advises that patients treated with some types of gene therapy undergo follow-up observations for potential adverse events for as long as 15 years. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. In addition, the holder of a BLA must comply with the FDA's advertising and promotion requirements, such as those related to the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"). Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, 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 or if a regulatory authority disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market, the institution of a REMS program or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of our product candidates, a regulatory or enforcement authority may:

- issue a warning letter asserting that we are in violation of the law;

- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of the product; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and adversely affect our business, financial condition, results of operations and prospects.

In addition, the FDA's policies, and those of the EMA and other regulatory authorities, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would negatively impact our business, financial condition, results of operations and prospects.

Even if we obtain and maintain approval for our product candidates in a major pharmaceutical market such as the United States, we may never obtain approval for our product candidates in other major markets.

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

We may seek a conditional marketing authorization in Europe for some or all of our current product candidates, but we may not be able to obtain or maintain such designation.

As part of its marketing authorization process, the European Commission may grant marketing authorizations for certain categories of medicinal products on the basis of less complete data than is normally required, when doing so may meet unmet medical needs of patients and serve the interest of public health. In such cases, it is possible for the

CHMP to recommend the granting of a marketing authorization, subject to certain specific obligations to be reviewed annually, which is referred to as a conditional marketing authorization. This may apply to medicinal products for human use that are subject to approval through the centralized process, including those that aim at the treatment, the prevention, or the medical diagnosis of seriously debilitating or life-threatening diseases and those designated as orphan medicinal products.

A conditional marketing authorization may be granted when the CHMP finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

- the risk-benefit balance of the medicinal product is positive;
- it is likely that the applicant will be in a position to provide the comprehensive clinical data;
- unmet medical needs will be fulfilled; and
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data is still required.

The granting of a conditional marketing authorization is restricted to situations in which only the clinical part of the application is not yet fully complete. Incomplete preclinical or quality data may only be accepted if duly justified and only in the case of a product intended to be used in emergency situations in response to public health threats. Conditional marketing authorizations are valid for one year, on a renewable basis. The holder will be required to complete ongoing trials or to conduct new trials with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

Granting a conditional marketing authorization allows medicines to reach patients with unmet medical needs earlier than might otherwise be the case and will ensure that additional data on a product is generated, submitted, assessed and acted upon. Although we may seek a conditional marketing authorization for one or more of our product candidates, the CHMP may ultimately not agree that the requirements for such conditional marketing authorization have been satisfied and hence delay the commercialization of our product candidates.

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

In the United States and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The MMA expanded Medicare coverage for outpatient drug purchases by adding a new Medicare Part D program and introduced a new reimbursement methodology based on average sales prices for Medicare Part B physician-administered drugs. In addition, the MMA authorized Medicare Part D prescription drug plans to limit the number of drugs that will be covered in any therapeutic class in their formularies. The MMA's cost reduction initiatives and other provisions could decrease the coverage and price that we receive for any approved products. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors. Similar regulations or reimbursement policies may be enacted in international markets which could similarly impact our business.

More recently, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or the PPACA, was passed, which substantially changes the way healthcare is financed by both the government and private insurers, and significantly impacts the U.S. pharmaceutical industry. The PPACA, among other things: (i) addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; (ii) increases the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and

extends the rebate program to individuals enrolled in Medicaid managed care organizations; (iii) establishes annual fees and taxes on manufacturers of certain branded prescription drugs; (iv) expands the availability of lower pricing under the 340B drug pricing program by adding new entities to the program; and (v) establishes a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (and 70% starting January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand 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. Additionally, in the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biologic products that are demonstrated to be "highly similar" (biosimilar) or "interchangeable" with an FDA-approved biologic product. This new pathway could allow competitors to reference data from biologic products already approved after 12 years from the time of approval. This could expose us to potential competition by lower-cost biosimilars even if we commercialize a product candidate faster than our competitors. Moreover, the creation of this abbreviated approval pathway does not preclude or delay a third party from pursuing approval of a competitive product candidate via the traditional approval pathway based on their own clinical trial data.

Additional changes that may affect our business include those governing enrollment in federal healthcare programs, reimbursement changes, rules regarding prescription drug benefits under the health insurance exchanges and fraud and abuse and enforcement. Continued implementation of the PPACA and the passage of additional laws and regulations may result in the expansion of new programs such as Medicare payment for performance initiatives, and may impact existing government healthcare programs, such as by improving the physician quality reporting system and feedback program.

For each state that does not choose to expand its Medicaid program, there likely will be fewer insured patients overall, which could impact the sales, business and financial condition of manufacturers of branded prescription drugs. Where patients receive insurance coverage under any of the new options made available through the PPACA, manufacturers may be required to pay Medicaid rebates on that resulting drug utilization. The U.S. federal government also has announced delays in the implementation of key provisions of the PPACA. The implications of these delays for our and our potential partners' business and financial condition, if any, are not yet clear.

In addition, there have been judicial and congressional challenges to certain aspects of the PPACA, and we expect the current administration and Congress will likely continue to seek legislative and regulatory changes, including repeal and replacement of certain provisions of the PPACA. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by President Trump on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain PPACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amends the PPACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". The Congress will likely consider other legislation to replace elements of the PPACA, during the next Congressional session.

The Trump Administration has also taken executive actions to undermine or delay implementation of the PPACA. In January 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the PPACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the PPACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In October 2017, the President signed a second Executive Order allowing for the use of association health plans and short-term health insurance, which may provide fewer health benefits than the plans sold through the PPACA exchanges. At the same time, the Trump Administration announced that it will discontinue the payment of cost-sharing reduction, or CSR, payments to insurance companies until Congress approves the appropriation of funds for such CSR payments. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA.

A bipartisan bill to appropriate funds for CSR payments was introduced in the Senate, but the future of that bill is uncertain. Further, in July 2018 following a federal district court decision form New Mexico, the Trump Administration announced that it would be freezing payments to insurers under the PPACA to cover sicker patients until it or Congress can address the appropriate methodology for calculating and making such payments. It remains to be seen how this action will affect the implementation of the PPACA.

We will continue to evaluate the effect that the PPACA and its possible repeal and replacement could have on our business. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace PPACA provisions is highly uncertain in many respects, it is also possible that some of the PPACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with PPACA coverage expansion provisions. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop commercialize product candidates.

Further, there have been several recent U.S. congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, the Trump Administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, individual states are increasingly aggressive 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. In addition, regional health care 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 health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

In addition, on May 11, 2018, the Trump Administration issued a plan to lower drug prices. Under this blueprint for action, the Trump Administration indicated that the Department of Health and Human Services, or HHS, will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases.

At the state level, individual states are increasingly aggressive 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. In addition, regional health care 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 health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Tax authorities may disagree with our positions and conclusions regarding certain tax positions, including research and development tax credits, resulting in unanticipated costs, taxes or non-realization of expected benefits.

A tax authority may disagree with tax positions including research and development tax credits, that we have taken, which could result in increased tax liabilities. For example, Her Majesty's Revenue & Customs, or HMRC, the U.S. Internal Revenue Service or another tax authority could challenge our allocation of income by tax jurisdiction and the amounts paid between our affiliated companies pursuant to our intercompany arrangements and transfer pricing policies, including amounts paid with respect to our intellectual property development. 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 contrast 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.

We are subject to the U.K. Bribery Act, the U.S. Foreign Corrupt Practices Act and other anti-corruption laws, as well as export control laws, import and customs laws, trade and economic sanctions laws and other laws governing our operations.

Our operations are subject to anti-corruption laws, including the U.K. Bribery Act 2010, or the Bribery Act, the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. §201, the U.S. Travel Act, and other anti-corruption laws that apply in countries where we do business. The Bribery Act, the FCPA and these other laws generally prohibit us and our employees and intermediaries from authorizing, promising, offering, or providing, directly or indirectly, improper or prohibited payments, or anything else of value, to government officials or other persons to obtain or retain business or gain some other business advantage. Under the Bribery Act, we may also be liable for failing to prevent a person associated with us from committing a bribery offense. We and our commercial partners operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we participate in collaborations and relationships with third parties whose corrupt or illegal activities could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws, even if we do not explicitly authorize or have actual knowledge of such activities. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United Kingdom and the United States, and authorities in the European Union, including applicable export control regulations, economic sanctions and embargoes on certain countries and persons, anti-money laundering laws, import and customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. Likewise, any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United Kingdom, United States or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

Our relationships with customers, physicians and third-party payors will be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, health information privacy and security laws and other healthcare laws and regulations. If we are found in violation of these laws and regulations, we may be required to pay a penalty or be suspended from participation in federal or state healthcare programs, which may adversely affect our business, financial condition and results of operations.

Our operations will be directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Anti-Kickback Statute, the federal civil and criminal laws and Physician Payments Sunshine Act and regulations. These laws will impact, among other things, our clinical research programs and proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. The laws that will affect our operations include, but are not limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, in return for either the referral of an individual, or the purchase, leasing, furnishing or arranging for the purchase, lease or order of a good, facility, item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers and formulary managers on the other. The PPACA amended the intent requirement of the federal Anti-Kickback Statute, such that a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it;
- federal civil and criminal false claims laws and civil monetary penalty laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid or other government payors that are false or fraudulent. The PPACA provides, and recent government cases against pharmaceutical and medical device manufacturers support the view that federal Anti-Kickback Statute violations and certain marketing practices, including off-label promotion, may implicate the False Claims Act;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes that prohibit, among other things, a person from knowingly and willfully executing a scheme or from making false or fraudulent statements to defraud any healthcare benefit program, regardless of the payor (e.g., public or private);
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, which impose certain requirements relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, such as health plans, health care clearinghouses and certain health care providers, and their respective business associates that perform certain functions or activities that involve the use or disclosure of protected health information on their behalf;
- federal transparency laws, including the federal Physician Payment Sunshine Act, that require certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the CMS information related to: (i) payments or other "transfers of value" made to physicians and teaching hospitals and (ii) ownership and investment interests held by physicians and their immediate family members; and
- state and foreign law equivalents of each of the above federal laws, state and local laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other

governmental regulations that may apply to us, we may be subject to significant criminal, civil and administrative sanctions including monetary penalties, damages, fines, disgorgement, individual imprisonment, and exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, reputational harm, and we may be required to curtail or restructure our operations, any of which could adversely affect our ability to operate our business and our results of operations.

The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. The shifting compliance environment and the need to build and maintain robust and expandable systems to comply with multiple jurisdictions with different compliance and/or reporting requirements increases the possibility that a healthcare company may run afoul of one or more of the requirements.

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the European Union. The provision of benefits or advantages to physicians is governed by the national laws of European Union Member States, including anti-bribery laws such as the UK Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment. Payments made to physicians in certain European Union Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual European Union Member States. These requirements are provided in the national laws, industry or health system codes or professional codes of conduct, applicable in the European Union Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the European Union General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with our activities in the European Union.

If we or our service providers fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur substantial costs.

We and our service providers are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the generation, handling, use, storage, treatment, manufacture, transportation and disposal of, and exposure to, hazardous materials and wastes, as well as laws and regulations relating to occupational health and safety. Our operations involve the use of hazardous and flammable materials, including chemicals and biologic materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our or our service providers' use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and

penalties. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

Although we maintain workers' compensation insurance for certain costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work related injuries, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for toxic tort claims that may be asserted against us in connection with our storage or disposal of biologic, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations, which have tended to become more stringent over time. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could adversely affect our business, financial condition, results of operations and prospects.

Risks Related to Our Business Operations

We may not be successful in our efforts to identify or discover additional product candidates and may fail to capitalize on programs or product candidates that may be a greater commercial opportunity or for which there is a greater likelihood of success.

The success of our business depends upon our ability to identify, develop and commercialize a pipeline of gene therapy treatments for rare inherited retinal diseases. Research programs to identify new product candidates require substantial technical, financial and human resources. Although certain of our product candidates are currently in clinical or preclinical development, we may fail to identify other potential product candidates for clinical development for several reasons. For example, our research may be unsuccessful in identifying potential suitable product candidates or our potential product candidates may be shown to have harmful side effects, may be commercially impracticable to manufacture or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

Additionally, because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our spending on current and future research and development programs may not yield any commercially viable products. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Alternatively, we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a partnering arrangement.

If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate, which could have a negative impact on our business, financial condition, results of operations and prospects.

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

We are highly dependent on members of our executive team, including David Fellows, our Chief Executive Officer, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time. We currently do not have "key person" insurance on any of our employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, also will be critical to our success. There currently is a shortage of skilled individuals with substantial gene therapy experience, which is likely to continue. As a result, competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies and academic institutions for individuals with similar skillsets. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. In addition, failure to succeed in preclinical studies or clinical trials or applications for marketing approval may make it more challenging to recruit and retain qualified personnel. The inability to recruit, or loss of services of certain executives, key employees, consultants or advisors, may impede the progress of our research, development and commercialization objectives and have an adverse effect on our business, financial condition, results of operations and prospects.

If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.

If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources to manage our operations, continue our research and development activities and, in the longer term, build a commercial infrastructure to support commercialization of any of our product candidates that are approved for sale. Future growth would impose significant added responsibilities on members of management, may lead to significant added costs, and may divert our management and business development resources. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and product candidates requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas and to attract and retain sufficient numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development, commercialization and growth goals.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with FDA or EMA regulations or the regulations applicable in other jurisdictions, provide accurate information to the FDA, EMA and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA, EMA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. While we have a code of business conduct and ethics applicable to all of our employees, it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent these activities may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations and prospects, including the imposition of significant criminal, civil and administrative sanctions, such as monetary penalties, damages, fines, disgorgement, individual imprisonment, and exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, reputational harm, and we may be required to curtail or restructure our operations.

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

We face an inherent risk of product liability exposure related to the testing of our current and future product candidates in clinical trials and may face an even greater risk if we commercialize any product candidate that we may develop. If we cannot successfully defend ourselves against claims that our product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidate that we may develop;
- loss of revenue;
- substantial monetary awards to trial participants or patients;
- significant time and costs to defend the related litigation;
- withdrawal or slower enrollment of clinical trial participants;
- the inability to commercialize any product candidates that we may develop; or
- injury to our reputation and significant negative media attention.

Although we maintain product liability insurance coverage, such insurance may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage each time we commence a clinical trial and if we successfully commercialize any product candidate. Insurance coverage is increasingly expensive. 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.

The United Kingdom's vote in favor of withdrawing from the European Union may have a negative effect on global economic conditions, financial markets and our business, which could reduce the market price of our ADSs and make it more difficult to do business in Europe.

In June 2016, the United Kingdom voted to withdraw from the European Union in a national referendum. The withdrawal of the United Kingdom from the European Union, commonly referred to as Brexit, is scheduled to take effect on March 29, 2019, although there may possibly be a transition period until December 31, 2020 while negotiations between the United Kingdom and European Union Member States take place to determine the future terms of the United Kingdom's relationship with the European Union.

The general speculation and uncertainty around Brexit has had and may continue to have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U.K. financial and banking markets, as well as on the regulatory process in Europe. As a result of this uncertainty, global financial markets could experience significant volatility, which could adversely affect the market price of our ADSs. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility. Lack of clarity about future laws and regulations in the U.K. as the United Kingdom determines which European Union rules and regulations to replace or replicate in the event of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, could decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict our access to capital. If the United Kingdom and the European Union are unable to negotiate acceptable withdrawal terms or if other European Union Member States pursue withdrawal, barrier-free access between the United Kingdom and other European Union Member States or among the European Economic Area overall could be diminished or eliminated.

We may also face new regulatory costs and challenges that could have an adverse effect on our operations as Brexit may change the legal framework applicable to our business. Depending on the terms of Brexit, the United Kingdom could lose the benefits of global trade agreements negotiated by the European Union on behalf of its members, which may result in increased trade barriers that could make our doing business in Europe more difficult. In

addition, currency exchange rates in the pound sterling and the euro with respect to each other and the U.S. dollar have already been adversely affected by Brexit. Furthermore, at present, there are no indications of the effect Brexit will have on the pathway to obtaining marketing approval for any of our product candidates in the United Kingdom, or what, if any, role the EMA may have in the approval process. Any delay in obtaining, or an inability to obtain, any marketing approvals as a result of Brexit or otherwise would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

Exchange rate fluctuations may materially affect our results of operations and financial condition.

Owing to the international scope of our operations, fluctuations in exchange rates, particularly between the pound sterling and the U.S. dollar, may adversely affect us. Although we are based in the United Kingdom, we source research and development, manufacturing, consulting and other services from the United States and the European Union. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates not only between the pound sterling and the U.S. dollar, but also the euro, which may have a significant impact on our results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place.

Exchange rate fluctuations between local currencies and the pound create risk in several ways, including the following:

- weakening of the pound may increase the pound-denominated cost of overseas research and development expenses and the cost of sourced product components outside of the U.K.;
- strengthening of the pound may decrease the value of our revenues denominated in other currencies;
- the exchange rates on non-pound transactions and cash deposits can distort our financial results; and
- commercial pricing and profit margins can be affected by currency fluctuations.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. The size and complexity of our information technology systems, and those of our collaborators, contractors and consultants, and the large amounts of confidential information stored on those systems, make such systems vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third-party vendors and/or business partners, or from cyber-attacks by malicious third parties. Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect or anticipate. Cyber-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 confidentiality, integrity and availability of information. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient.

While we have not experienced a system failure, accident, cyber-attack or security breach that has resulted in a material interruption in our operations to date, if such an event were to occur, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Additionally, any such event that leads to unauthorized access, use or disclosure of personal information, including personal information regarding our patients or employees, could harm our reputation

or competitive position, require to expend significant capital and other resources to address the breach, cause us not to comply with federal and/or state breach notification laws and foreign law equivalents and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information. Security breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above. While we have implemented security measures to protect our information technology systems and infrastructure, there can be no assurance that such measures will prevent service interruptions or security breaches that could adversely affect our business and the further development and commercialization of our product candidates could be delayed.

Risks Related to Ownership of Our Securities

The price of our ADSs may be volatile and may fluctuate substantially due to factors beyond our control.

The trading price of our ADSs has fluctuated and is likely to continue to fluctuate significantly. The market price of our ADSs depends on a number of factors, some of which are beyond our control, including limited trading volume. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this Report on Form 6-K, these factors include:

- the commencement, enrollment or results of our planned and future clinical trials, as well as positive or negative results from, delays in, such testing or clinical trials;
- the loss of any of our key scientific or management personnel;
- announcements of the failure to obtain regulatory approvals or receipt of warning letters from the FDA, EMA or other regulatory agency;
- announcements of undesirable restricted labeling indications or patient populations, or changes or delays in regulatory review processes;
- announcements of innovations or new products by us or our competitors;
- adverse actions taken by regulatory agencies with respect to our clinical trials, manufacturing supply chain or sales and marketing activities;
- changes or developments in laws or regulations applicable to our product candidates;
- any changes to our relationships with licensors, collaborators, manufacturers or suppliers, including the commencement, termination, and success of future collaborations;
- the failure of our testing and clinical trials or of those of our competitors;
- unanticipated safety concerns;
- announcements concerning our competitors or the pharmaceutical industry in general;
- the achievement of expected product sales and profitability;
- the ability to obtain third-party reimbursements for our product candidates;
- manufacture, supply or distribution shortages;
- actual or anticipated fluctuations in our operating results;
- the level of expenses related to any of our product candidates or clinical development programs;
- our cash position;
- changes in financial estimates or recommendations by securities analysts, including publication of research reports or comments by securities or industry analysts;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- potential acquisitions, financings or other corporate transactions;

- the trading volume of our ADSs on Nasdaq;
- sales of our ADSs by us, our executive officers and directors or our shareholders in the future;
- general economic, political, and market conditions and overall fluctuations in the financial markets, and specifically the pharmaceutical and biotechnology sectors, in the United States or the United Kingdom;
- changes in accounting principles; and
- other events and factors, including those described elsewhere in this "Risk Factors" section, many of which are beyond our control.

In addition, the stock market in general, and Nasdaq and biopharmaceutical companies in particular, have experienced significant price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of particular companies. Broad market and industry factors may negatively affect the market price of our ADSs, regardless of our actual operating performance. Further, a decline in the financial markets and related factors beyond our control may cause the price of our ADSs to decline rapidly and unexpectedly. You may not realize any return on your investment in us and may lose some or all of your investment.

Substantial future sales of our ADSs, or the perception that these sales could occur, could cause the price of the ADSs to decline.

Additional sales of our ADSs, or the perception that these sales could occur, could cause the market price of the ADSs to decline. If any of our large shareholders or members of our management team sell substantial amounts of ADSs in the public market, or the market perceives that such sales may occur, the market price of our ADSs and our ability to raise capital through an issue of equity securities in the future could be adversely affected.

An active trading market for our common stock may not be sustained.

Our ADSs began trading on the Nasdaq Global Select Market in September 2017. Given the limited trading history of our shares, there is a risk that an active trading market may not continue to develop or be sustained. If an active market for our ADSs does not continue to develop or is not sustained, it may be difficult for you to sell shares or ADSs without depressing the market price for the shares, or at all.

Our ADSs will not be traded on any exchange outside of the United States.

Our ADSs are listed only in the United States on the Nasdaq Global Select Market, and we have no plans to list the ADSs or our ordinary shares in any other jurisdiction. As a result, a holder of ADSs outside of the United States may not be able to effect transactions in the ADSs as readily as the holder may if our securities were listed on an exchange in that holder's home jurisdiction.

Shareholder protections and restrictions found in provisions under The City Code on Takeovers and Mergers do not apply to us.

In March 2018, the UK Takeover Panel confirmed that we are not considered to be subject to The City Code on Takeovers and Mergers, or The Takeover Code, and, as a result, our shareholders are not entitled to the benefit of certain takeover offer protections provided under The Takeover Code. The Takeover Code provides a framework within which takeovers of companies are regulated and conducted and which may operate to prohibit certain arrangements and courses of conduct considered customary in the United States. There are no provisions in our Articles of Association which replicate the provisions of The Takeover Code.

We believe that this position is unlikely to change at any time in the near future, but in accordance with good practice, we will review the situation on a regular basis and co-operate and consult with the UK Takeover Panel if there is any material change in our circumstances with respect to matters which the UK Takeover Panel might consider relevant in their determination of jurisdiction over us.

The significant share ownership position of our executive officers, directors and principal shareholders may limit your ability to influence corporate matters.

As of August 31, 2018, our executive officers and directors, combined with our affiliated shareholders who owned more than 5% of our outstanding ADSs or ordinary shares and their respective affiliates, in the aggregate, beneficially owned ordinary shares representing approximately 67.6% of our outstanding share capital. As a result, if these shareholders were to choose to act together, they would be able to control all matters submitted to our shareholders for approval, as well as our management and affairs. These shareholders either alone or voting together as a group may be in a position to determine or significantly influence the outcome of decisions taken at any such general meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our general meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members and the approval of certain significant corporate transactions. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management and the board of directors; or
- impede a merger, consolidation, takeover or other business combination involving us that other shareholders may desire.

Any of these consequences could adversely affect the market price of our ADSs.

We have broad discretion in the use of our available cash and other sources of funding and may not use them effectively.

Our management has broad discretion in the use of our available cash, cash equivalents and marketable securities and could spend those resources in ways that do not improve our results of operations or enhance the value of our ADSs. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our ADSs to decline and delay the development and commercialization of our product candidates. We may invest our available cash and cash equivalents, pending their use, in a manner that does not produce income or that loses value.

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

We are incorporated under English law. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of ADSs, are governed by English law, including the provisions of the U.K. Companies Act 2006, or the Companies Act, and by our Articles of Association. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations.

Holders of our ADSs may not have the same voting rights as the holders of our ordinary shares and may not receive voting materials in time to be able to exercise their right to vote.

Holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares evidenced by the ADSs on an individual basis. The depositary or its nominee will act as the representative for the holders of the ADSs and will exercise the voting rights attached to the ordinary shares represented by the ADSs. Holders of our ADSs may not receive voting materials in time to instruct the depositary to vote, and it is possible that they, or persons who hold their ADSs through brokers, dealers or other third parties, will not have the opportunity to exercise a right to vote. Furthermore, the depositary will not be liable for any failure to carry out any instructions to vote, for the manner in which any vote is cast or for the effect of any such vote. As a result, holders of our ADSs may not be able to exercise voting rights and may lack recourse if their ADSs are not voted as requested. In addition, holders of our ADSs will not be able to call a shareholders' meeting.

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

The depositary for the ADSs has agreed to pay to holders of our ADSs 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. Holders of our ADSs will receive these distributions in proportion to the number of our ordinary shares their 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 the ADSs. We have no obligation to take any other action to permit distribution on the ADSs, ordinary shares, rights or anything else to holders of the ADSs. This means that holders of our ADSs may not receive the distributions we make on our ordinary shares or any value from them if it is unlawful or impractical to make them available to you. These restrictions may have an adverse effect on the value of the ADSs.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be our ADS holders' and shareholders' sole source of gains and they may never receive a return on their investment.

Under current English law, a company's accumulated realized profits must exceed its accumulated realized losses (on a non-consolidated basis) before dividends can be paid. Therefore, we must have distributable profits before issuing a dividend. We have not paid dividends in the past on our ordinary shares. We intend to retain earnings, if any, for use in our business and do not anticipate paying any cash dividends in the foreseeable future. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, on our ADSs will be our ADS holders' sole source of gains for the foreseeable future, and they will suffer a loss on their investment if they are unable to sell their ADSs at or above the price at which they purchased the ADSs.

If we engage in future acquisitions or strategic partnerships, this may increase our capital requirements, dilute our shareholders, cause us to incur debt or assume contingent liabilities and subject us to other risks.

We intend to continue to evaluate various acquisitions and strategic partnerships, including licensing or acquiring complementary drugs, intellectual property rights, technologies or businesses. Any potential acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent liabilities;
- assimilation of operations, intellectual property and drugs of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing development programs and initiatives in pursuing such a strategic partnership, merger or acquisition;
- retention of key employees, the loss of key personnel and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing drugs or drug candidates and regulatory approvals; and
- our inability to generate revenue from acquired technology and/or product candidates sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

Any or all of these risks could have an adverse effect on our business, financial condition, results of operations and prospects.

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 U.S. public companies. This may limit the information available to holders of our ADSs.

We are a "foreign private issuer," as defined in the SEC rules and regulations and, consequently, we are not subject to all of the disclosure requirements applicable to companies organized within the United States. For example, we are exempt from certain rules under the U.S. 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. In addition, our officers 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, we are not required to file periodic reports and financial statements with the SEC as frequently or as promptly as U.S. public companies. Accordingly, there may be less publicly available information concerning our company than there is for U.S. public companies. As such, our shareholders may not be afforded the same protections or information generally available to investors holding shares in public companies organized in the United States.

We have determined that, as of June 30, 2018, we no longer qualified as a foreign private issuer under the rules and regulations of the SEC. We made the determination based on the fact that, as of June 30, 2018, more than 50 percent of our outstanding voting securities were directly or indirectly owned of record by residents of the United States and a majority of our executive officers were U.S. citizens or residents. As a result, beginning January 1, 2019, we anticipate that our future annual filings with the SEC will be made on Form 10-K (including our annual report for the year ending December 31, 2018) rather than on Form 20-F. In addition, commencing on January 1, 2019, we plan to expand our reporting consistent with that of a domestic U.S. filer, including filing quarterly reports on Form 10-Q and current reports on Form 8-K. We will also be subject to SEC rules governing the solicitation of proxies, consents or authorizations in respect of a security registered under the Securities Exchange Act of 1934, or the Exchange Act; the provisions of Regulation Fair Disclosure, which regulate the selective disclosure of material information; and the sections of the Exchange Act requiring insiders to file public reports of their share ownership and trading activities and establishing insider liability for profits realized from any "short-swing" transactions in our equity securities. In addition, beginning January 1, 2019, we will also be subject to the Nasdaq Stock Market listing requirements applicable to domestic U.S. issuers.

We expect that the loss of foreign private issuer status will increase our legal and financial compliance costs and make some activities highly time consuming and costly. We also expect that it will be more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our board of directors.

While we are a foreign private issuer, we are not subject to certain Nasdaq corporate governance rules applicable to U.S. listed companies.

As a foreign private issuer, we are entitled to rely on a provision in Nasdaq's corporate governance rules that allows us to follow English corporate law and the Companies Act with regard to certain aspects of corporate governance. This allows us to follow certain corporate governance practices that differ in significant respects from the corporate governance requirements applicable to U.S. companies listed on Nasdaq. A foreign private issuer that elects to follow a home country practice instead of Nasdaq requirements must submit to Nasdaq in advance a written statement from an independent counsel in such issuer's home country certifying that the issuer's practices are not prohibited by the home country's laws. In addition, a foreign private issuer must disclose in its Annual Reports filed with the SEC each such requirement that it does not follow and describe the home country practice followed instead of any such requirement.

For example, we are exempt from Nasdaq regulations that require a listed U.S. company to (i) have a majority of the board of directors consist of independent directors, (ii) require non-management directors to meet on a regular basis without management present and (iii) promptly disclose any waivers of the code for directors or executive officers that should address certain specified items.

In accordance with our Nasdaq listing, our audit committee is required to comply with the provisions of Section 301 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and Rule 10A-3 of the Exchange Act, both of which are also applicable to Nasdaq-listed U.S. companies. Because we are a foreign private issuer, however, our audit committee is not subject to additional Nasdaq requirements applicable to listed U.S. companies, including an affirmative determination that all members of the audit committee are "independent," using more stringent criteria than those applicable to us as a foreign private issuer. Furthermore, Nasdaq's corporate governance rules require listed U.S. companies to, among other things, seek shareholder approval for the implementation of certain equity compensation plans and issuances of ordinary shares, which we are not required to follow as a foreign private issuer.

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

We are an "emerging growth company," or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an EGC, we may take advantage of 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 of the Sarbanes-Oxley Act, or Section 404, exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved, and reduced disclosure obligations regarding executive compensation. As an EGC, we are required to report only two years of financial results and selected financial data compared to three and five years, respectively, for comparable data reported by other public companies. We may take advantage of these exemptions until we are no longer an EGC. We could be an EGC until December 31, 2022, although circumstances could cause us to lose that status earlier, including if the aggregate market value of our ADSs held by non-affiliates exceeds $700 million as of June 30 (the end of our second fiscal quarter) of any fiscal year before that time or if we have annual gross revenues of $1.07 billion or more in any fiscal year, in which case we would no longer be an EGC as of December 31 (our fiscal year-end) of such fiscal year. We cannot predict if investors will find our ADSs less attractive because we may rely on these exemptions. If some investors find our ADSs less attractive as a result, there may be a less active trading market for our ADSs and the price of our ADSs may be more volatile.

In addition, the JOBS Act also provides that an EGC can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an EGC to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to delay such adoption of new or revised accounting standards, and, as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for public companies that are not EGCs.

If we fail to establish and maintain proper internal controls, our ability to produce accurate financial statements or comply with applicable regulations could be impaired. As a result, holders of our securities could lose confidence in our financing and other public reporting, which would harm our business and the trading price of our ADSs.

Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, is designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations.

Section 404(a) of the Sarbanes-Oxley Act, or Section 404(a), requires that beginning with our second annual report following our initial public offering, management assess and report annually on the effectiveness of our internal control over financial reporting and identify any material weaknesses in our internal control over financial reporting. Although Section 404(b) of the Sarbanes-Oxley Act, or Section 404(b), requires our independent registered public accounting firm to issue an annual report that addresses the effectiveness of our internal control over financial reporting, we have opted to rely on the exemptions provided in the JOBS Act, and consequently will not be required to comply with SEC rules that implement Section 404(b) until such time as we are no longer an EGC or otherwise exempt from such requirement.

We expect our first Section 404(a) assessment will take place for our annual report for the fiscal year ending December 31, 2018. The presence of material weaknesses could result in financial statement errors which, in turn, could lead to errors in our financial reports, delays in our financial reporting, which could require us to restate our operating results or our auditors may be required to issue a qualified audit report. We might not identify one or more material weaknesses in our internal controls in connection with evaluating our compliance with Section 404(a). To maintain and improve the effectiveness of our disclosure controls and procedures and internal control over financial reporting, we will need to expend significant resources and provide significant management oversight. Implementing any appropriate changes to our internal control may require specific compliance training of our directors and employees, entail substantial costs 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 maintaining the adequacy of our internal control.

If either we are unable to conclude that we have effective internal control over financial reporting or, at the appropriate time, our independent auditors are unwilling or unable to provide us with an unqualified report on the effectiveness of our internal control over financial reporting as required by Section 404(b), investors may lose confidence in our operating results, the price of our 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, we may not be able to remain listed on Nasdaq.

We previously identified a material weakness in our internal control over financial reporting. We may identify further material weaknesses in our internal control over financial reporting for future fiscal years. If we do not remediate material weaknesses or are unable to implement and maintain effective internal control over financial reporting in the future, the accuracy and timeliness of our financial reporting may be adversely affected.

Our management and independent registered public accounting firm previously identified a deficiency that was concluded to represent a material weakness in our internal control over financial reporting attributable to our lack of sufficient financial reporting and accounting personnel. SEC guidance regarding management's report on internal control over financial reporting defines a material weakness as a deficiency or combination of deficiencies in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected and corrected on a timely basis. This finding relates to our internal control infrastructure as of December 31, 2016 and 2015 where we did not design or implement sufficient processes, controls and other review procedures to evaluate the recognition and accrual of expenses for periods ended December 31, 2016 and 2015. As a result, there were adjustments required in connection with closing our books and records and preparing our 2016 and 2015 financial statements.

In response to the material weakness, we hired a full-time Chief Financial Officer in April 2017. We have hired and intend to hire additional finance and accounting personnel with appropriate expertise to perform specific functions, and design and implement improved processes and internal controls, build our financial management and reporting infrastructure and further develop and document our accounting policies and financial reporting procedures, including ongoing senior management review and audit committee oversight.

While we believe we have remediated the previously identified material weakness, we may discover future deficiencies in our internal controls over financial reporting, including those identified through testing conducted by us or subsequent testing by our independent registered public accounting firm. More generally, if we are unable to meet the demands that have been placed upon us as a public company, including the requirements of the Sarbanes-Oxley Act, we may be unable to accurately report our financial results in future periods, or report them within the timeframes required by law or stock exchange regulations. Failure to comply with the Sarbanes-Oxley Act, when and as applicable, could also potentially subject us to sanctions or investigations by the SEC or other regulatory authorities. Any failure to maintain or implement required new or improved controls, or any difficulties we encounter in their implementation, could result in additional material weaknesses or significant deficiencies, cause us to fail to meet our reporting obligations or result in material misstatements in our financial statements. Furthermore, if we cannot provide reliable financial reports or prevent fraud, our business and results of operations could be harmed and investors could lose confidence in our reported financial information.

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

As a U.S. public company, and particularly after we no longer qualify as an EGC, we will incur significant legal, accounting and other expenses that we did not incur previously. The Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of Nasdaq and other applicable securities rules and regulations impose various requirements on non-U.S. reporting public companies, including the establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our senior management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, these rules and regulations make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified senior management personnel or members for our board of directors.

However, these rules and regulations are often 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.

Pursuant to Section 404, we will be required to furnish a report by our senior management on our internal control over financial reporting. However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Claims of U.S. civil liabilities may not be enforceable against us or certain of our executive officers, directors, or experts.

We are incorporated under English law. Certain members of our board of directors and senior management are non-residents of the United States, and all or a substantial portion of our assets and the assets of such persons are located outside the United States. As a result, it may not be possible to serve process on such persons or us in the United States or to enforce judgments obtained in U.S. courts against them or us based on civil liability provisions of the securities laws of the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce judgments obtained in U.S. courts against them or us, including judgments predicated upon the civil liability provisions of the U.S. federal securities laws.

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

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

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

Under the Internal Revenue Code of 1986, as amended, or the Code, we will be a passive foreign investment company, or PFIC, for any taxable year in which (1) 75% or more of our gross income consists of passive income or (2) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as if it held its proportionate share of the assets and received directly its proportionate share of the income of such other corporation. If we are a PFIC for any taxable year during which a U.S. Holder (as defined in our Annual Report for the fiscal year ended December 31, 2017 under "Item 10.E. Taxation—Material U.S. Federal Income Tax Considerations for U.S. Holders") holds our shares, 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.

Although we believe that it is more likely than not that we were not a PFIC for our taxable year ended December 31, 2017, and that it is more likely than not that we will not be a PFIC for our current taxable year or future taxable years, we cannot provide any assurances regarding our PFIC status for any past, current or future taxable years. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis and the applicable law is subject to varying interpretation. In particular, the characterization of our assets as active or passive may depend in part on our current and intended future business plans, which are subject to change. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income, which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by how, and how quickly, we spend the cash we raise in any offering.

For further discussion of the PFIC rules and the adverse U.S. federal income tax consequences in the event we are classified as a PFIC, see the section of our Annual Report for the fiscal year ended December 31, 2017, titled "Item 10.E. Taxation—Material U.S. Federal Income Tax Considerations for U.S. Holders."

Recent and future changes to tax laws could materially adversely affect our company and reduce net returns to our shareholders

Our tax treatment is subject to changes in tax laws, regulations and treaties, or the interpretation thereof and the practices of tax authorities in jurisdictions in which we operate. Future changes, and thus our future tax treatment, may be affected by various tax policy initiatives and reforms under consideration, as well as tax policy initiatives and reforms related to the Organisation for Economic Co-Operation and Development's, or OECD, Base Erosion and Profit Shifting, or BEPS, Project, the European Commission's state aid investigations and other initiatives. 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. In addition, the impact of U.S. tax legislation enacted near the end of 2017 (H.R. 1, "An Act to provide for reconciliation pursuant to titles II and V of the concurrent resolution on the budget for fiscal year 2018", informally referred to as the Tax Cuts and Jobs Act, or the Tax Act), on our business and financial condition remains uncertain and could have an adverse effect on that condition.

We are unable to predict what tax laws, regulations, policies or practices may be enacted or adopted in the future in various jurisdictions where we have operations, or what effect such changes would have on our business. Such changes may affect our future effective tax rates in those jurisdictions and have an adverse effect on our overall effective tax rate and also may increase the complexity, burden and cost of tax compliance.

We may be unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments or benefit from favorable U.K. tax legislation.

As a U.K. resident trading entity, we are subject to U.K. corporate taxation. Due to the nature of our business, we have generated losses since inception. As of December 31, 2017, we had cumulative carryforward tax losses of $37.9 million. Subject to any relevant restrictions, we expect these to be available to carry forward and offset against future operating profits. As a company that carries out extensive research and development activities, we benefit from the U.K. research and development tax credit regime for small and medium-sized companies, whereby we are able to surrender the trading losses that arise from our qualifying research and development activities for a payable tax credit of up to 33.35% of eligible research and development expenditures. Qualifying expenditures largely comprise employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects. Certain subcontracted qualifying research expenditures are eligible for a cash rebate of up to 21.67%. The majority of our pipeline research, clinical trials management and manufacturing development activities are eligible for inclusion within these tax credit cash rebate claims. For example, our eligibility to claim payable research and development tax credits may be limited or eliminated if we no longer qualify as a small or medium-sized company.

We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenues from patented products to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenues and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the U.K. research and development tax credit regime or the "patent box" regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments then our business, results of operations and financial condition may be adversely affected.