C. Reasons for the Offer and Use of Proceeds

Not applicable.

D. Risk Factors

Our business faces significant risks and uncertainties. You should carefully consider all of the information set forth in this Annual Report and in other documents we file with or furnish to the Securities and Exchange Commission, or SEC, including the following risk factors, before deciding to invest in or to maintain an investment in our securities. Our business, as well as our reputation, financial condition, results of operations, and share price, could be materially adversely affected by any of these risks, as well as other risks and uncertainties not currently known to us or not currently considered material.

Summary of Selected Risks Associated with Our Business

- The development and commercialization of pharmaceuticals and biologics is highly competitive. In particular, RUCONEST® faces competition from other products (acute and prophylactic) used to treat Hereditary Angioedema, or HAE, including products to prevent and treat HAE attacks. There are several products from other competitors that have been approved in the U.S. and Europe for the treatment of HAE attacks. Consequently, we may not obtain sufficient market penetration with RUCONEST® or a sufficient level of sales of the product to remain profitable.
- We are heavily dependent on sales of RUCONEST® in the United States and Europe. If we are unable to continue to commercialize RUCONEST®, our business could be materially harmed.
- Joenja® is a newly approved drug in the U.S. and could develop unexpected safety or efficacy concerns, which would likely have a material adverse effect on us.
- The commercial success of our approved products depends, and the commercial success of any product candidate will depend, upon the degree of market acceptance by physicians, patients, payors and others in the medical community.
- If we are unable to maintain and grow our sales and marketing capabilities, particularly outside of the United States, or enter into agreements with third parties to market and sell our products outside of the United States and Europe, our business will be adversely affected.
- Revenue from our approved products depends, and the successful commercialization of our product candidates will depend, in part, on the extent to which governmental authorities and health insurers maintain or establish, as applicable, adequate coverage, reimbursement levels and pricing policies. Failure to maintain or obtain coverage and adequate reimbursement for our approved products and our product candidates, if approved, could limit our ability to market those products and decrease revenue generating ability.
- Since many of our product candidates are at an early stage of development, 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 than our current product candidates due to limited resources available.
- The costs and timing of potential clinical trials, filings and approvals, and the potential therapeutic scope of the development and commercialization of our products involve a high degree of uncertainty and risk which make it difficult to predict the time and costs of product development of novel approaches.
- We rely on third parties for the conduct of significant aspects of our preclinical studies and clinical trials and intend to rely on third parties in the future. If these third parties do not successfully carry out their contractual duties, our business may be adversely impacted.
- We conduct clinical trials for certain of our product candidates at sites outside the United States. The U.S. Food and Drug Administration, or the FDA, may not accept data from trials conducted in such locations.
- We may not be able to obtain or maintain orphan drug exclusivity for our products or product candidates. If our competitors are able to obtain orphan drug exclusivity for their products, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.
- The results from our clinical trials may not be sufficiently robust to support the submission of marketing approval for our product candidates. Before we submit our product candidates for marketing

approval, the FDA and/or the European Medicines Agency, or the EMA, may require us to conduct additional clinical trials or evaluate patients for an additional follow-up period.

- We depend on our information technology systems and have been and may in the future be the victim of cyberattacks which compromise the privacy, security, integrity or confidentiality of sensitive information related to our business or prevent us from accessing critical information and expose us to liability and reputational harm, which could adversely affect our business, results of operations and financial condition.
- Any contamination in the manufacturing process for our recombinant products, 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 and significantly impact commercially available goods.
- We are dependent on a limited number of suppliers for some of the components and materials used in our product candidates and product. Any disruption in the supply of these materials could adversely affect our ability to deliver product or complete clinical trials. Other studies of product candidates, regulatory applications or commercializing product candidates in a timely and commercially valuable manner, may be adversely affected, should supply be disrupted.
- We depend on third-party manufacturers for the production of Joenja® and for the production of rhC1INH for commercial supply and for use in clinical trials of RUCONEST®, as well as our product candidates for clinical trials. Interruption in supply could materially and adversely affect sales.
- We experience significant customer concentration, with a limited number of customers accounting for a significant portion of our revenues.
- Our success is dependent on our ability to obtain and protect rights to proprietary technology and to develop our technology and products without infringing the proprietary rights of third parties.
- Our patents may be challenged, deemed unenforceable, invalidated or circumvented, and if we do not obtain or maintain patent protection for the products, our business may be materially harmed.
- There are material weaknesses in our internal control over financial reporting and if we are unable to remediate them, or if we identify additional material weaknesses in the future or otherwise fail to maintain an effective system of internal control, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect our business and stock price.
- Our business and operations may be negatively impacted by the failure, or perceived failure, of achieving environmental, social and governance, or ESG, objectives.

Risks Related to Our Business

The development and commercialization of pharmaceuticals and biologics is highly competitive. In particular, RUCONEST® faces intense competition from other products used to treat Hereditary Angioedema, or HAE. Several products have been approved in the U.S. and Europe for the treatment of HAE attacks. Consequently, we may not obtain sufficient market penetration with RUCONEST® or a sufficient level of sales of the product to remain profitable.

The development and commercialization of pharmaceuticals and biologics is highly competitive. In particular, RUCONEST® faces intense competition from other products used to treat HAE. We face the risk that RUCONEST® may no longer be competitive and accepted by physicians, patients, payors and others in the medical community within acute HAE market. Prophylactic therapies are increasingly used, which may result in HAE patients requiring less acute rescue medicine. RUCONEST® is not approved for prophylactic use.

Several products have been approved in the U.S. and Europe for the treatment of HAE attacks, including human blood plasma derived C1INH products. Oral products for the prevention of HAE attacks are also being developed. Orladeyo® (berotralstat) is an oral prophylactic product which was approved in the fourth quarter of 2020. In the acute market, we face pricing competition as a result of the 2019 market entry of generic equivalents to the acute treatment: Firayzr® (icatibant injection). Consequently, we may not obtain sufficient market penetration with RUCONEST® or a sufficient level of sales of the product to allow it to remain profitable. New technologies from competitors may make RUCONEST® obsolete.

Our competitors include major international pharmaceutical companies as well as smaller or regional specialty pharmaceutical and biotechnology companies. Many of our competitors are larger and have greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, prosecuting intellectual property rights and marketing approved products

than we do. Such competitors may be better equipped to withstand changes in economic and industry conditions. Smaller or early stage companies may also be significant competitors, particularly through collaborative arrangements with large, established companies. Key competitive factors affecting the commercial success of our products and any other products that we develop or acquire are likely to be safety, efficacy, tolerability profile, reliability, convenience of dosing, price and reimbursement. We may also face future competition from companies selling generic alternatives to RUCONEST® in countries where we do not have patent coverage, orphan drug status or another form of data or marketing exclusivity or where patent coverage or data or marketing exclusivity has expired, is not enforced, or may, in the future, be challenged.

We are heavily dependent on sales of RUCONEST® in the United States and Europe. If we are unable to continue to commercialize RUCONEST®, our business could be materially harmed.

We have, to date, been substantially focused on the development and commercialization of RUCONEST®, and we expect to continue to be dependent primarily on revenues from RUCONEST® sales in the near term. Although we have begun sales of Joenja® in the United States, RUCONEST® sales accounted for approximately 92.6% of our total revenues in 2023, and we expect it to continue to make up the majority of our revenues for the foreseeable future. Accordingly, any adverse events or findings regarding the properties, efficacy or safety of RUCONEST®, or material constraints on the manufacturing of RUCONEST®, may have a material impact on our financial results and operations.

Our ability to meet expectations with respect to sales of RUCONEST®, generate revenues from such sales, and attain and maintain positive cash flow from operations, in the time periods anticipated, or at all, will depend on a number of factors, including, among others:

- the ability to continue to maintain and grow market acceptance for RUCONEST® among healthcare professionals and patients in the United States, EU, and other key markets for the treatment of approved indications;
- our ability to maintain regulatory approvals without onerous restrictions or limitations in key markets;
- our ability to secure regulatory approvals in additional markets on a timely basis and with commercially feasible labels;
- our ability to obtain pricing and reimbursement approvals at adequate levels, where required, on a timely basis;
- presence of side effects or other safety issues associated with the use of RUCONEST® that could require us or our distributors to modify or halt commercialization;
- whether we will be required by regulatory agencies to conduct additional studies regarding the safety and efficacy of RUCONEST®, which we have not planned or anticipated;
- increased competition from competitors;
- obtaining and maintaining commercial distribution agreements with third-party distributors outside the United States and Europe;
- obtaining and maintaining patent protection and regulatory exclusivity; and adequately investing in the manufacturing, sales, marketing, market access, medical affairs and other functions that are supportive of our commercialization efforts.

Joenja® is a newly approved drug in the U.S. and could develop unexpected safety or efficacy concerns, which would likely have a material adverse effect on us.

Joenja® was granted approval by the FDA in late March 2023. In the United States, Joenja® will now be used by larger numbers of patients, potentially for longer periods of time, and we and others (including regulatory agencies and private payors) will collect extensive information on the efficacy and safety of Joenja® by monitoring its use in the marketplace. New safety or efficacy data from market surveillance may result in negative consequences including the following:

- Modification to product labeling or promotional statements, such as additional boxed or other warnings or contraindications, or the issuance of additional “Dear Doctor Letters” or similar communications to healthcare professionals;
- Required changes in the administration of Joenja®;

- Imposition of additional post-marketing surveillance, post-marketing clinical trial requirements, distribution restrictions or other risk management measures, such as a risk evaluation and mitigation strategy;
- Suspension or withdrawal of regulatory approval or delays or declination of regulatory approval outside of the United States;
- Suspension of, or imposition of restrictions on, our operations, including costly new manufacturing requirements with respect to Joenja®; and
- Voluntary or mandatory product recalls or withdrawals from the market and costly product liability claims.

Any of these circumstances could reduce Joenja's® market acceptance and would be likely to materially adversely affect our business.

The commercial success of our approved products depends, and the commercial success of any product candidate will depend, upon the degree of market acceptance by physicians, patients, payors and others in the medical community.

The commercial success of our approved products depends, and of our product candidates will depend, in part, on the medical community, patients, and payors accepting them as effective, safe and cost-effective. If our product candidates do not achieve an adequate level of acceptance, we may struggle to continue to generate significant product revenues and may not in the future generate any profits from operations. The degree of market acceptance of our approved products, in particular Joenja®, or our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments;
- the frequency and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the frequency and severity of any side effects resulting from the conditioning regimen or follow-up requirements for the administration of our product candidates;
- the relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments;
- continued demand from two U.S. specialty wholesale companies that in 2023 represented 83% of our revenues; and
- sufficient third-party insurance coverage or reimbursement.

Even if a product candidate displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product, if approved for commercial sale, will not be known until after it is launched. Our efforts to educate the medical community and payors on the benefits of our products, particularly Joenja® given its recent approval, and product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors.

If we are unable to maintain and grow our sales and marketing capabilities, particularly outside of the United States, or enter into agreements with third parties to market and sell our products outside of the United States and Europe, our business will be adversely affected.

We have been promoting RUCONEST® in Europe and the Middle East since we re-acquired the license in 2020 and are currently preparing for the launch of leniolisib in Europe, the U.K., the Middle East, Africa, and Asia-Pacific. Establishing and maintaining internal medical and commercial capabilities, as we are doing for Joenja®, carries an element of risk. For example, recruiting and training an integrated medical and commercial organization can be expensive and time consuming and could delay any product launch. Furthermore, if the commercialization of a product is delayed, , establishing a commercial organization prematurely would result in the need to reconfigure the organization.

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

- the inability to recruit, train and retain adequate numbers of effective medical, access, sales and marketing personnel;
- inability to obtain appropriate regulatory approval and subsequent reimbursement coverage
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future product that we may develop;
- 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.

We enter into arrangements with a variety of third-parties to perform a range of activities including medical affairs, regulatory and reimbursement support and, sales, marketing and distribution services outside of the United States and Europe. We have made leniolisib available for APDS patients in select key markets in Europe, the U.K., Japan, Asia-Pacific, the Middle East, and Canada. Where viable, following regulatory approval, we intend to market leniolisib directly in a number of these markets. Prior to regulatory approval in certain markets, we will make leniolisib available via a variety of access schemes. In addition, we have granted the China State Institute of Pharmaceutical Industry, or the CSIPI, an exclusive license to commercialize RUCONEST® in China, and the CSIPI is collaborating with the Chengdu Institute of Biological Products Co, Ltd, or the CDIBP,and we are solely dependent on their efforts to commercialize RUCONEST® in that territory. On December 15, 2023, the CDIBP announced that it received clinical trial approval from the Center for Drug Evaluation of the National Medical Product Administration for the clinical development of rhC1INH in China. We may receive certain regulatory and manufacturing-associated milestones, and we are eligible to receive low to mid-single digit royalties from sales in China by the CSIPI, affiliates of the CSIPI and sublicencees of the CSIPI. Dependence on distribution arrangements to commercialize our products in certain jurisdictions subjects us to a number of risks. We do not have control over such third parties and any of them may fail to devote the necessary resources and attention to distribute our products effectively. In addition, any potential non-compliance with applicable laws and regulations by such third parties would potentially expose us to sanctions. If such third-party arrangements are terminated or allowed to expire, the marketing and sales of a product in that jurisdiction may be interrupted, which could adversely affect our revenues. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. See “Item 3 – D. Risk Factors – We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic markets. We can face criminal liability and other serious consequences for violations, which can harm our business” of this Annual Report.

Revenue from our approved products depends, and the successful commercialization of our product candidates will depend, in part, on the extent to which governmental authorities and health insurers maintain or establish, as applicable, adequate coverage, reimbursement levels and pricing policies. Failure to maintain or obtain coverage and adequate reimbursement for our approved products and our product candidates, if approved, could limit our ability to market those products and decrease revenue generating ability.

The availability and adequacy of coverage and reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third-party payors is essential for many patients to be able to afford prescription medications such as RUCONEST® and Joenja® and potential product candidates, assuming regulatory approval is obtained. Our ability to achieve acceptable levels of coverage and reimbursement for products by governmental authorities, private health insurers and other organizations fundamentally impacts the potential success of RUCONEST® and Joenja® and potential product candidates. Assuming we obtain coverage for our product candidates by third-party payors, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. We cannot be sure that coverage and reimbursement in the United States, the EU Member States, or elsewhere will be maintained for our approved products or available for our product candidates or any product that we may develop, and any reimbursement that may be or become available may be decreased or eliminated in the future. There is an increasing tendency of health insurers to reduce healthcare costs by limiting both the coverage and breadth of reimbursement for new therapeutic products and in some cases by refusing to provide coverage altogether.

Because coverage and reimbursement determinations are made on a payor-by-payor basis, obtaining coverage and adequate reimbursement from a third-party payor does not guarantee that we will obtain similar coverage or reimbursement from another third-party payor. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any products for which we obtain marketing approval. Failure to secure or retain adequate coverage or reimbursement for our products by third-party payors, or delays in processing approvals by those payors, could result in the loss of sales, loss of customers, or reputational damage, which could have a material adverse effect on our business, financial condition and operating profit.

Further, it is possible that a third-party payor may consider our product candidates as similar to alternative treatment options and only offer to reimburse patients for a less expensive product. In some cases this can involve a requirement that patients try the less expensive product first, only approving other therapies after the patient does poorly on the less expensive product. Even if we show improved efficacy or convenience of administration with our product candidates compared to products marketed by our competitors and the prevailing standard of care, the pricing of existing therapies may still limit the amount we could charge. Third-party payors may deny or revoke the reimbursement status of any given product or establish new prices for existing marketed products that inhibit us from realizing an appropriate return on our investment in the product candidates. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our product candidates, and may not be able to obtain a satisfactory financial return on them.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada, and other countries has and will continue to put pressure on the pricing and usage of our products. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. Other countries allow companies to set 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 products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

Since many of our product candidates are at an early stage of development, 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 than our product candidates due to limited resources available.

Other than Joenja®, which was approved by the FDA on March 24, 2023, our product pipeline candidates are all in the early stages of clinical and preclinical development. For example, our gene therapy product candidate is in preclinical development. Our spending on current and future research and development programs may not yield any commercially viable product candidates. 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 collaborations, 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. 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.

The costs and timing of potential clinical trials, filings and approvals, and the potential therapeutic scope of the development and commercialization of our products involve a high degree of uncertainty and risk which make it difficult to predict the time and costs of product development of novel approaches.

New product development and indication expansions of existing products is very expensive and involves a high degree of uncertainty and risk. Only a small number of research and development programs result in the commercialization of a new product. Furthermore, the development of novel approaches for the treatment of diseases, including development efforts in new and innovative modalities present additional challenges and risks. Clinical trial data and results are subject to differing interpretations by regulatory authorities. We may view data as sufficient to support the safety, effectiveness, or approval of an investigational therapy, while regulatory authorities may disagree and may require additional data, may limit the scope of an approval

or may deny approval altogether. There can be difficulty in predicting the time and cost of product development of novel approaches for the treatment of diseases across regulatory approval authorities.

Success in preclinical work or early-stage clinical trials does not ensure that later stage or larger scale clinical trials will be successful. The results of clinical trials may indicate that our product candidates lack efficacy, have harmful side effects, result in unexpected adverse events or raise other concerns that may significantly reduce the likelihood of regulatory approval. This may result in terminated programs, significant restrictions on use and safety warnings in an approved label, adverse placement within the treatment paradigm or significant reduction in the commercial potential of the product candidate.

Even if we could successfully develop new products or indications, we may make a strategic decision to discontinue development of a product candidate or indication if, for example, we believe commercialization will be difficult relative to the standard of care or other opportunities in our pipeline.

We rely on third parties for the conduct of significant aspects of our preclinical studies and clinical trials and intend to rely on third parties in the future. If these third parties do not successfully carry out their contractual duties, our business may be adversely impacted.

We rely on third parties for the conduct of significant aspects of our preclinical studies and clinical trials. These third parties include contract research organizations, or CROs, medical institutions, clinical investigators and contract laboratories. Although we design the clinical trials for our product candidates, we depend on these third parties for aspects of performing the trials. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our regulatory or contractual responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial.

The third parties we rely upon may fail to successfully carry out their contractual duties or meet expected deadlines, which may cause delays in the conduct of our preclinical and clinical studies.

If the CROs do not perform preclinical studies and clinical trials in a satisfactory manner, breach their obligations to us or fail to comply with regulatory requirements and other compliance obligations, the development, regulatory approval and commercialization of our product candidates may be delayed, we may not be able to obtain regulatory approval and commercialize our product candidates, or our development programs may be materially and irreversibly harmed. If we are unable to rely on preclinical and clinical data collected by our CROs, we could be required to repeat, extend the duration of, or increase the size of any clinical trials we conduct and this could significantly delay commercialization and require significantly greater expenditures. See “Item 3 – D. Risk Factors – We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic markets. We can face criminal liability and other serious consequences for violations, which can harm our business” of this Annual Report.

We conduct clinical trials for certain of our product candidates at sites outside the United States. The FDA may not accept data from trials conducted in such locations.

We and the investigators conducting clinical trials for certain of our product candidates study our product candidates outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful.

In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and would delay or permanently halt our development of the applicable product candidates or indications. In addition, in order to commence a clinical trial in the United States, we are required to seek FDA acceptance of an Investigational New Drug application, or IND, for each of our product candidates. We cannot be certain that any IND we submit to the

FDA, or any similar Clinical Trial Application, or CTA, we submit in other countries, will be accepted. We may also be required to conduct additional preclinical testing prior to submitting an IND for any of our product candidates, and the results of any such testing may not be positive. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to a New Drug Application, or NDA, or Biologics License Application, or BLA, submission and approval of our product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing our product candidates.

We may not be able to obtain or maintain orphan drug exclusivity for our products or product candidates. If our competitors are able to obtain orphan drug exclusivity for their products, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time.

Regulatory authorities in some jurisdictions, including the United States, the EU and the United Kingdom, may designate drugs for relatively small patient populations as orphan drugs. We obtained orphan drug designation for RUCONEST® from the FDA for the treatment of acute HAE attacks. Joenja® has also received this designation from the FDA and the EMA. However, no assurances can be made for our product candidates.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of market exclusivity, which, subject to certain exceptions, precludes the acceptance or approval by a regulatory authority in the EU of another marketing application for a similar medicinal product or the approval by the FDA of another marketing application for the same drug for the same indication for that time period. The FDA defines “same drug” as a drug or biologic that contains the same active moiety and is intended for the same use. The applicable market exclusivity period for orphan drugs is ten years in the EU and the United Kingdom and seven years in the United States. The EU and United Kingdom exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation.

In the EU and the United Kingdom, a “similar medicinal product” is a medicinal product containing a similar active substance or substances as contained in a currently authorized orphan medicinal product, and which is intended for the same therapeutic indication. A “similar active substance” is “an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism. However, in the case of advanced therapy medicinal products, for which the principal molecular structural features cannot be fully defined, the similarity between two active substances shall be assessed on the basis of the biological and functional characteristics.” Obtaining orphan drug exclusivity for our product candidates is important to the product candidate’s success. If a competitor obtains orphan drug exclusivity for, and approval of, a product with the same indications as our product candidates before we do and if the competitor’s product is the same drug or a similar medicinal product as ours, we could be excluded from the market for a certain period of time. If another product has obtained a marketing authorization for the same indication, we would have to prepare a similarity report (addressing the possible similarity between the authorized product and our product), which will take additional time.

Although we have obtained orphan drug exclusivity for Joenja® from the FDA, the EMA, and the Ministry of Health, Labour and Welfare of Japan, or MHLW, we may not be able to maintain it. For example, if a competitive product that is the same drug or a similar medicinal product as our product or product candidate is shown to be clinically superior to our product or product candidate, as applicable, any orphan drug exclusivity we have obtained will not block the approval of such competitive product. In addition, orphan drug exclusivity will not prevent the approval of a product that is the same drug as our product or product candidate if the FDA, EMA or United Kingdom’s Medicines and Healthcare products Regulatory Agency, or MHRA, finds that we cannot assure the availability of sufficient quantities of the drug to meet the needs of the persons with the disease or condition for which the drug was designated in the relevant jurisdiction.

The FDA Reauthorization Act of 2017 authorizes the FDA to impose additional clinical trial requirements on manufacturers seeking orphan drug designation and/or pediatric indications. Additionally, it should be noted that the European Commission is currently reviewing the EU general pharmaceutical legislation. While any revisions to the legislation will not be applicable for a number of years, the European Commission intends to

make changes to the rules on orphan medicinal products including potentially reducing the duration of data and market exclusivity available.

The results from our clinical trials may not be sufficiently robust to support the submission of marketing approval for our product candidates. Before we submit our product candidates for marketing approval, the FDA, the EMA, or any other regulatory body may require us to conduct additional clinical trials or evaluate patients for an additional follow-up period.

The results from our clinical trials may not be sufficiently robust to support the submission for marketing approval for our product candidates. The FDA normally requires two registrational trials to approve a drug or biologic product, and thus the FDA may require that we conduct additional clinical trials of our product candidates prior to a BLA or NDA submission. The FDA typically does not consider a single clinical trial to be adequate to serve as a registrational trial unless among other things, it is well-controlled and demonstrates a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, and a confirmatory study would be practically or ethically impossible. Additionally, while the FDA recognizes the potential for natural history models to augment the need for placebo arms in trials for drugs that target very rare disease, where trial recruitment can be especially challenging, the FDA has found the use of natural history data as a historical comparator to be unsuitable for adequate and well-controlled trials in many circumstances. The FDA generally finds trials using historical controls to be credible only when the observed effect is large in comparison to variability in disease course. Like the FDA, the EMA and MHRA also expect applicants to submit sufficient clinical data, which is usually generated from clinical studies, to demonstrate the safety and efficacy of the medicinal product.

Due to the nature of the indications our product candidates are designed to treat, and the limited number of patients with these conditions, a placebo-controlled and blinded study may not be practicable for ethical and other reasons. It is possible the FDA, EMA and/or MHRA will not consider our comparisons to natural history data and, where available, historical transplant data, to provide clinically meaningful results. Additionally, even though a product candidate may have achieved the primary endpoints in a registrational clinical trial, it is possible that the FDA, EMA and/or MHRA may require us to conduct additional registrational trials, possibly involving a larger sample size or a different clinical trial design, especially if the FDA, EMA and/or MHRA do not find the results from these trials to be sufficiently persuasive to support a BLA/NDA or Marketing Authorization Application, or MAA, submission, as applicable. The FDA, EMA and/or MHRA may also require that we conduct a longer follow-up period of post-market surveillance of patients treated with our product candidates prior to accepting our BLA/NDA or MAA submission, as applicable.

In addition, data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. There can be no assurance that the FDA, EMA or other regulatory bodies will find the efficacy endpoints in our registrational trials or any efficacy endpoint we propose in future registrational trials to be sufficiently validated and clinically meaningful, or that our product candidates will achieve the pre-specified endpoints in current or future registrational trials to a degree of statistical significance, and with acceptable safety profiles. We also may experience regulatory delays or rejections as a result of many factors, including serious adverse events involving our product candidates, changes in regulatory policy or changes in requirements during the period of our product candidate development. Any such delays could materially and adversely affect our business, financial condition, results of operations and prospects.

We expect that the FDA, EMA and/or MHRA will assess the totality of the safety and efficacy data from our product candidates in reviewing any future BLA, NDA, or MAA, submissions. Based on this assessment, the FDA, EMA and/or MHRA may require that we conduct additional preclinical studies or clinical trials prior to submitting or approving a BLA, NDA, or MAA, for our target indications.

If the FDA, EMA and/or MHRA requires additional trials, we would incur increased costs and delays in the marketing approval process, which may require us to expend more resources than we have available. In addition, it is possible that the FDA, EMA and/or MHRA may have divergent opinions on the elements necessary for a successful BLA/NDA and MAA, respectively, which may cause us to alter our development, regulatory and/or commercialization strategies.

Any future acquisitions we make may expose us to risks that could adversely affect our business, and we may not achieve the anticipated benefits of acquisitions of businesses or technologies.

As a part of our growth strategy, we may make additional acquisitions of complementary businesses, products or research. Any future acquisition will involve numerous risks and operational, financial and managerial challenges, including the following, any of which could adversely affect our business, financial condition or results of operations:

- limited support and user knowledge for legacy systems of acquired companies;
- problems maintaining uniform procedures, controls and policies with respect to our financial accounting systems;
- difficulties in managing geographically dispersed operations, including risks associated with entering foreign markets in which we have no or limited prior experience;
- underperformance of any acquired technology, product or business relative to our expectations and the price we paid;
- negative near-term impacts on financial results after an acquisition, including acquisition-related earnings charges;
- the potential loss of key employees, customers and strategic partners of acquired companies;
- claims by terminated employees and shareholders of acquired companies or other third parties related to the transaction;
- the assumption or incurrence of additional debt obligations or expenses, or use of substantial portions of our cash;
- the issuance of equity securities to finance or as consideration for any acquisitions that dilute the ownership of our shareholders;
- any collaboration, strategic alliance and licensing arrangement may require us to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms that are not favorable to us;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products or product candidates and regulatory approvals;
- diversion of management’s attention and company resources from existing operations of the business;
- inconsistencies in standards, controls, procedures and policies;
- the impairment of intangible assets as a result of technological advancements, or worse-than-expected performance of acquired companies;
- assumption of, or exposure to, historical liabilities of the acquired business, including unknown contingent or similar liabilities that are difficult to identify or accurately quantify;
- our inability to generate revenues from acquired technology or products sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs; and
- risks associated with acquiring intellectual property, including potential disputes regarding acquired companies’ intellectual property.

There can be no assurance that any of the acquisitions we may make will be successful or will be, or will remain, profitable. Our failure to successfully address the foregoing risks may prevent us from achieving the anticipated benefits from any acquisition in a reasonable time frame, or at all.

Negative public opinion and increased regulatory scrutiny of transgenic manufacturing techniques, or activism regarding the ethical treatment of livestock, may damage public perception of RUCONEST® and our product candidates, which may adversely affect sales of our products and our ability to obtain marketing approvals for our product candidates.

Public perception may be influenced by negative public statements regarding our transgenic manufacturing technology. Our transgenic manufacturing technology platform involves the genetic engineering of animals for the production of recombinant proteins. Genetic modification of food and livestock are a common subject of debate and negative publicity. In addition, animal rights activists commonly engage in campaigns to reduce or eliminate the use of animals in the commercialization of pharmaceutical products.

Negative publicity regarding genetic modification in general, and our transgenic manufacturing techniques in particular, or activism regarding the treatment of our livestock could result in reduced market acceptance for our products, increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product

candidates that are approved and a decrease in demand for any such product candidates. If any such adverse events occur, commercialization of RUCONEST® or further advancement of our clinical trials could be halted or delayed, which would have a material adverse effect on our business and operations.

Our assumptions and estimates regarding prevalence and the addressable markets for our products and product candidates may be inaccurate, which could have a material adverse effect on our revenues and cash position.

If there are fewer actual patients than estimated, or if any product approval is based on narrower definitions of patient populations, our revenues and cash position could be materially and adversely affected. The patient population for the diseases that our products treat is very small, and networking, data gathering and support channels are not as established as those for more prevalent and researched disease indications. There are limited patient registries and other methods of establishing with precision the actual number of patients of our existing and potential future indications in any geography. Estimating the prevalence of a rare disease is difficult and we therefore must rely on assumptions, beliefs and an amalgam of information from multiple sources, resulting in potential under or over-reporting. There is no guarantee that our assumptions and beliefs are correct, or that the methodologies used and data collected have generated or will continue to generate accurate estimates. There is therefore uncertainty around the estimated total potential addressable patient population for treatment with RUCONEST® and Joenja® worldwide. In addition, the potential market opportunity for our product candidates that we may develop is difficult to estimate precisely, particularly given that the orphan drug markets which are targeted are, by their nature, relatively unknown. Our estimates of the potential market opportunity for each of these product candidates are predicated on several key assumptions, such as industry knowledge and publications, third-party research reports and other surveys. If any of our assumptions prove to be inaccurate, then the actual market for RUCONEST®, Joenja®, or our product candidates, could be smaller than our estimates of the potential market opportunity. If that turns out to be the case, our product revenue may be limited, and we may be unable to achieve or maintain profitability, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

We depend on our information technology systems have been and may in the future be the victim of cyberattacks, which compromise the privacy, security, integrity or confidentiality of sensitive information related to our business or prevent us from accessing critical information and expose us to liability and reputational harm, which could adversely affect our business, results of operations and financial condition.

We collect and maintain data and information that is necessary to conduct our business, and we are increasingly dependent on information technology systems and infrastructure to operate our business, including systems infrastructure operated and maintained by our third-party suppliers or providers. In the ordinary course of our business, we collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information. It is critical that we do so in a secure manner to maintain the privacy, security, confidentiality and integrity of such confidential information. We have established physical, electronic and organizational measures to safeguard and secure our systems and facilities to prevent an information compromise, and rely on commercially available systems, software, tools and monitoring to provide security for our information technology systems and the processing, transmission and storage of digital information. We have also outsourced elements of our information technology infrastructure, and as a result, a number of third-party vendors may or could have access to our confidential information. Our internal information technology systems and infrastructure, and those of our current and any future collaborators, contractors and consultants and other third parties on which we rely, are vulnerable to damage or unauthorized access or use resulting from computer viruses, malware, natural disasters, terrorism, war, telecommunication and electrical failures, denial-of-service attacks, cyber-attacks or cyber-intrusions over the Internet, hacking, phishing and other social engineering attacks, attachments to emails, persons inside our organization (including employees or contractors), lost or stolen devices, or persons with access to systems inside our organization. We have been, and may in the future be, subject to cyberattacks.

A breach may require notification to governmental agencies, supervisory bodies, credit reporting agencies, the media or individuals pursuant to various federal, state and foreign data protection, privacy and security laws, regulations and guidelines, if applicable. These may include state breach notification laws, and the General Data Protection Regulation, or GDPR. Accordingly, a data security breach or privacy violation that leads to unauthorized access to, disclosure or modification of personal information (including protected health information), that prevents access to personal information or materially compromises the privacy, security, or

confidentiality of the personal information, could result in fines, increased costs or loss of revenue and we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed. Furthermore, federal, state and international laws and regulations, such as the GDPR, can expose us to enforcement actions and investigations by regulatory authorities, and potentially result in regulatory penalties and significant legal liability, if our information technology security efforts fail.

We rely on third parties for all quality control procedures.

The release of finished product to the market is dependent on the satisfaction of a set of quality control procedures. Some of these procedures, although validated, are very sensitive and complex (specifically for the protein platform). While ensuring and maintaining Good Manufacturing Practice, or GMP, activities at our partnered contract manufacturing organization, or CMO, sites we do not have our own GMP certified analytical laboratory capable of performing the quality control procedures needed for the release of product, and we rely on third parties for this task. We have started a program to challenge and reassess all currently used quality control procedures with the aim to improve or replace those by more robust, and easier to perform analyses and where possible create a more robust external partnership management process.

Any contamination in the manufacturing process for our recombinant products, 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 and significantly impact commercially available goods.

We use living mammals as the source for our recombinant proteins. Our transgenic manufacturing platform bears the risk of failure due to contamination of the produced milk, diseases of the producing livestock, or a breakdown of the facilities. Any contamination could adversely affect our ability to produce, release, or administer our recombinant products on schedule and could, therefore, harm our results of operations and cause reputational damage. Additionally, although our recombinant products are tested for contamination prior to release, if a contaminated product was administered to a patient, it could result in harm to the patient. A raw material shortage, contamination, recall or restriction on the goods we use in the manufacture of our products could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could adversely affect our clinical development timelines and availability of finished goods for commercial use, impacting patient access, our business, financial condition, results of operations, and prospects.

We are dependent on a limited number of suppliers for some of our components and materials used in our product candidates and products. Any disruption in the supply of these materials could adversely affect our ability to deliver product or complete clinical trials. Other studies of product candidates, regulatory applications or commercializing product candidates in a timely and commercially valuable manner, may be adversely affected, should supply be disrupted.

We rely on a limited number of suppliers for certain essential materials incorporated into, or used in the manufacture of, products and product candidates. Since RUCONEST® is authorized for use in rare and ultra-rare diseases, it might be difficult to find suppliers that can or are willing to handle small-scale quantities, which may also limit our negotiation power with these suppliers.

Many component suppliers are based in Europe, while a significant percentage of RUCONEST® sales are conducted in the U.S. If international shipping is disrupted, we may not be able to supply sufficient quantities of RUCONEST® for sale in the U.S. Any disruption in the supply of these materials could adversely affect our ability to deliver product or complete clinical trials. In addition, studies of product candidates, regulatory applications and our ability to commercialize product candidates in a timely and commercially valuable manner, may be adversely affected, should supply be disrupted.

We cannot be sure that these suppliers will remain in business, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to produce these materials for our intended purpose. Our use of a limited number of suppliers of raw materials, components and finished goods exposes us to several risks, including disruptions in supply, price increases, late deliveries and an inability to meet customer demand. There are, in general, relatively few alternative sources of supply for these components. These vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components could take a substantial amount of time and it may be

difficult to establish replacement suppliers who meet regulatory requirements. Any disruption in supply from any supplier or manufacturing location could lead to supply delays or interruptions which would damage our business, financial condition, results of operations and prospects.

If we are required to switch to a replacement supplier, the manufacture and delivery of our product and product candidates could be interrupted for an extended period, adversely affecting our business. Establishing additional or replacement suppliers may not be accomplished quickly. If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. For example, the FDA or EMA could require additional supplemental data, manufacturing data and comparability data if we rely upon a new supplier. While we seek to maintain adequate inventory of the components and materials used in our product candidates, any interruption or delay in the supply of components or materials, or our inability to obtain components or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to conduct our clinical trials and, if our product candidates are approved, to meet the demand of our customers and cause them to cancel orders.

In addition, as part of the FDA's approval of our product candidates, the FDA must review and approve the individual components of our production process, which includes raw materials, the manufacturing processes and facilities of our suppliers. Our reliance on these suppliers subjects us to a number of risks that could harm our reputation, business, and financial condition, including, among other things:

- the interruption of supply resulting from modifications to or discontinuation of a supplier's operations;
- delays in product shipments resulting from defects, reliability issues, or a supplier's variation in a component;
- a lack of long-term supply arrangements for key components with our suppliers;
- the inability to obtain adequate supply in a timely manner, or to obtain adequate supply on commercially reasonable terms;
- difficulty and cost associated with locating and qualifying alternative suppliers for our components in a timely manner;
- production delays related to the evaluation and testing of products from alternative suppliers, and corresponding regulatory qualifications;
- a delay in delivery due to our suppliers prioritizing other customer orders over ours;
- damage to our reputation caused by defective components produced by our suppliers; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

If any of these risks materialize, costs could significantly increase and our ability to conduct our clinical trials and meet demand for our products could be impacted.

We depend on third-party manufacturers for the production of Joenja® and for the production of rhC1INH for commercial supply and for use in clinical trials of RUCONEST®, as well as our product candidates for clinical trials. Interruption in supply could materially and adversely affect sales.

We have entered into (downstream) manufacturing and supply agreements for Joenja® and RUCONEST® with, among others, Sanofi S.A., or Sanofi, and BioConnection Investments B.V. (formerly BioConnection B.V.), or BioConnection, since we do not have a GMP-certified lab capable of performing the quality control procedures necessary for the release of product. A failure of these suppliers to supply our needs would be difficult to overcome as contracting additional manufacturing capacity on a timely basis could be difficult or impossible and have significant adverse effect on our business.

We experience significant customer concentration, with a limited number of customers accounting for a significant portion of our revenues.

Two U.S. customers (namely specialty pharmacies) accounted for $204.3 million, or 83%, of our revenues for the year ended December 31, 2023 and $173.6 million, or 84%, of our revenues for the year ended December 31, 2022. Inherent risks exist when a large percentage of total revenues is concentrated with a limited number of specialty pharmacies. With specialty products, the pharmacies provide patient support services that are more than are provided by retail pharmacies, and effective communication and relations between our hub and these pharmacies are important in maintaining timely and consistent filling of prescriptions for RUCONEST®.

It is not possible for us to predict the future level of demand for our products that will be handled by these specialty pharmacies or the level of service they will provide to patients and healthcare practitioners. In addition, revenues from these large customers may fluctuate from time to time based on market demand for our products among prescribing physicians, patients and payors, the level which may be affected by market conditions or other factors, some of which may be outside of our control. Further, our contracts with these large specialty pharmacies do not contain purchase commitments or otherwise obligate them to buy a minimum or fixed volume of products from us (and allow these specialty pharmacies to return product to us for a variety of reasons). If either of our major customers experience declining or delayed sales of our products to consumers due to market, economic or competitive conditions, we could be pressured to reduce the prices we charge for our products, reduce the volume of products we supply to such customers, we could lose the customer or have a substantial amount of product returned to us. Additionally, although historically, our reserves for doubtful accounts have not been material, if either of our large customers were to suffer financial instability, they could refuse or delay payment of outstanding receivables. Any such development may have a material adverse effect on our business, results of operations and financial condition.

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

Our future success depends on our ability to attract and retain key management personnel and scientific and technical personnel. Experienced employees in the biopharmaceutical and biotechnology industries are in high demand and competition for their talents can be intense, especially in The Netherlands, where we maintain our principal operations. We have entered into employment agreements with executive officers and other key employees, but any employee may terminate his or her employment at any time or may be unable to continue in his or her role. The loss of any executive or key employee, or an inability to recruit desirable candidates or find adequate third parties to perform such services on reasonable terms and on a timely basis, could have a material adverse effect on our business, financial condition, results of operations and prospects. If we are not able to attract, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that could significantly impede our ability to achieve our development and commercial objectives, our ability to raise additional capital and our ability to implement our business strategy.

Our business, products or product pricing could be subject to negative publicity, which could have a material adverse effect on our reputation, business, financial position, results of operations, liquidity and cash flows.

In recent years, the pharmaceutical industry has been the subject of public complaints and significant publicity regarding the pricing of pharmaceutical products, including publicity and pressure resulting from prices charged by competitors and peer companies for new products as well as price increases by competitors and peer companies on older products that the public has deemed excessive. We may experience downward pricing pressure on the price of RUCONEST®, Joenja® and any other future approved products due to social or political pressure to lower the cost of drugs, which could reduce our revenue and future profitability. Orphan drugs in particular have received recent negative publicity for the perceived high prices charged for them by their manufacturers, and as a result orphan drug developers such as us may be negatively impacted by such publicity and any U.S. or other government regulatory response. Due to these factors, we may suffer public criticism and negative publicity in media coverage, by industry trade associations and legislators.

Any of the events or developments described above could result in reputational harm and reduced market acceptance and demand for our products, could harm our ability to market our products in the future, could cause us to incur significant expense, could cause our senior management to be distracted from execution of our business strategy, and could have a material adverse effect on our business, reputation, financial condition, results of operations, liquidity, cash flows, and/or share price.

Future legislation regarding energy consumption and waste regulations might hamper efficiency of our operations.

Our facilities consume a significant amount of electricity in connection with the operation of our business and our production processes have a high consumption of consumables and liquid process waste. While we proactively improve processes where feasible with the aim to reduce use of energy and reduce the consumption of materials, our efforts to reduce energy consumption may not be successful. Additionally, we process waste

such as chemicals for cleaning equipment (which need to be neutralized before disposing), milk waste, and fluids containing heavy metals. Legislation related to waste regulations or legislation requiring our facilities to reduce our energy consumption may have a material impact on our business.

Risks Related to Intellectual Property

Our success is dependent on our ability to obtain and protect rights to proprietary technology and to develop our technology and products without infringing the proprietary rights of third parties.

We rely, and will continue to rely, on a combination of patents, trademarks and confidentiality agreements with employees, consultants, collaborators, advisors and other third parties to protect the intellectual property related to our current and future product candidates. We use patents and licensing to protect our products and technology. We try to be careful to develop products that don't infringe on the proprietary rights of third parties. Currently, we have several patent applications granted and pending in countries including the U.S., Europe and Japan. The patent positions of pharmaceutical companies can be uncertain and may involve complex legal and factual questions.

The patents that we own and have license rights to now or the patents and patent applications that we may own or in-license in the future may not have patentable claims that protect our current and future product candidates in the relevant jurisdictions where we intend to commercialize such products. There is no assurance that we are aware of all potentially relevant prior art relating to current patents or current or future patent applications. As such, patent examiners may find prior art that can prevent a patent from issuing from a pending patent application. During the patent examination process, we may be required to narrow the pending claims to overcome prior art, a process that may limit the scope of patent protection. Even if patents do successfully issue based on our future patent applications, and even if the issued patents cover our current and future product candidates, including their compositions, formulation, method of manufacture, and method of use, third parties may challenge our issued patents' validity, enforceability or scope, which may result in such patents being narrowed so that they no longer cover competitors' products that are considered to infringe, invalidated or held unenforceable. Any successful opposition to these patents or any other patents owned by or licensed to us in the future could deprive us of rights necessary for the successful commercialization of any of our current or future product candidates, if approved. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be further reduced.

If the patent applications we may own or in-license with respect to our current and future product candidates fail to issue, if their breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for any of our current or future product candidates, it could dissuade other companies from collaborating with us to develop future product candidates, and threaten our ability to commercialize our current and future product candidates. Notably, pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Any such outcome could have an adverse effect on our business.

Moreover, our technologies and products may infringe on third-party intellectual property rights. As a result, we may face litigation or other legal proceedings concerning such intellectual property. These processes can be time-consuming and costly. In the event of an unfavorable ruling in patent or intellectual property litigation, we could be subject to significant liabilities to third parties, or be required to cease developing, manufacturing or selling the affected products or technology. Each of these outcomes may adversely affect our financial position. We may also be confronted with claims which are raised with the main aim of exploiting the nuisance value of publicly raised claims. In order to prevent the infringement of third-party intellectual property rights, we may need to acquire licenses for patents held by third parties to re-establish or maintain freedom to operate for our products, possibly on unfavorable terms. A failure to obtain licenses for patents held by third parties, or failure to obtain them on favorable terms, may have a material adverse effect on our financial and operational position.

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. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than U.S. law does. Furthermore, publications of discoveries in scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until

18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. 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 patent protection.

In addition, if the breadth or strength of protection provided by our patents and patent applications, whether owned or in-licensed now or in the future, is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our licensed patents may be challenged in the courts or patent offices in the United States. Such challenges may result in loss of exclusivity or in patent claims being narrowed so that they no longer cover competitors' products that are considered to infringe, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or unduly limit the duration of the patent protection of our technology and products. Moreover, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after the filing of the earliest non-provisional application to which the patent claims priority. Various extensions may be available; however, the exclusivity and protection afforded by a patent is limited. We may be required to disclaim a portion of patent term in order to overcome double patenting rejections from the patent office, thus potentially shortening our exclusivity period. Without patent protection for our current or future product candidates, we may be open to competition from generic versions of such products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

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

Competitors may infringe or otherwise violate our patents, the patents of our licensors or our other intellectual property rights. To counter infringement or unauthorized use, we may be required to file legal claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that an asserted patent is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that the asserted patent does not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of asserted patents at risk of being invalidated or interpreted narrowly and could put a related patent application at risk of not issuing. The initiation of a claim against a third party may also cause the third party to bring counter claims against us such as claims asserting that our patents are invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or lack of statutory subject matter. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant material information from the U.S. Patent and Trademark Office, or the USPTO, or made a materially misleading statement, during prosecution. Third parties may also raise similar validity claims before the USPTO in post-grant proceedings such as ex parte re-examinations, inter partes review, or post-grant review, or oppositions or similar proceedings outside the United States, in parallel with litigation or even outside the context of litigation. Third parties may also make it more difficult to obtain patents to our valuable technologies by engaging in pre-issuance submissions of prior art to the USPTO and in analogous proceedings in other jurisdictions. The outcome following legal assertions of invalidity and unenforceability is unpredictable. We cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. For the patents and patent applications that we may license in the future, we may have limited or no right to participate in the defense of any licensed patents against challenge by a third party. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of any future patent protection on our current or future product candidates. Such a loss of patent protection could harm our business.

We may not be able to detect or prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States. Our business could be harmed if in litigation the prevailing party does not offer us a license on commercially reasonable terms. Any litigation or other proceedings to enforce our intellectual property rights may fail, and even if successful, may result in substantial costs and distract our management and other employees.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have an adverse effect on the price of our ordinary shares.

We may infringe or be alleged to infringe the intellectual property rights of others, which may prevent or delay product development and commercialization efforts, requiring us to expend resources on litigation or other resolutions, which may materially and adversely affect our business.

Our success depends, in part, on our ability to operate without infringing the intellectual property rights and other proprietary rights of third parties. Identification of third-party patent rights that may be relevant to our products and proprietary technology is difficult because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty and uncertainty in assessing the meaning or scope of protection of patent claims. There could be issued patents of which we are or were not aware that our products infringe. There also could be patents that we believe we do not infringe, but that we may ultimately be found to infringe. Moreover, patent applications are in some cases maintained in secrecy until patents are issued. The publication of discoveries in the scientific or patent literature frequently occurs substantially later than the date on which the underlying discoveries were made and patent applications were filed. Because patents can take many years to issue, there may be currently pending applications of which we are unaware that may later result in issued patents that our products infringe. For example, pending applications may exist that provide support or can be amended to provide support for a claim that results in an issued patent that our product infringes. We may also be confronted with claims which are raised with the main aim of exploiting the nuisance value of publicly raised claims.

Proceedings involving our patents or patent applications or those of others could:

- put one or more of our patents at risk of being invalidated, rendered unenforceable or interpreted narrowly so that they no longer cover competitors' products that are considered to infringe;
- adversely impact the patentability of our inventions relating to our products;
- result in monetary damages, injunctive relief or otherwise harm our competitive position, including by limiting or terminating marketing and selling activities, increasing the risk for generic competition, limiting development and commercialization activities or requiring us to obtain licenses to use the relevant technology (which licenses may not be available on commercially reasonable terms, if at all); and
- otherwise negatively impact the enforceability, validity or scope of protection offered by the patents relating to the products.

We may not have the resources to adequately defend such claims, and even if successful in any such proceedings, we would incur substantial costs and divert management's time and attention in pursuing these proceedings, putting further strain on our resources, which could have a material adverse effect on our business, financial condition, results of operations and prospects. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court or other venue. Patent litigation is costly and time consuming. We may not have sufficient resources to bring these actions to a successful conclusion.

In addition, if we do not obtain a license, develop or obtain non-infringing technology, fail to defend an infringement action successfully or have infringed patents declared invalid, we may:

- incur substantial monetary damages;

- encounter significant delays in expanding the market of our products; and
- be precluded from manufacturing or selling any products; which, in each case, could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our patents may be challenged, deemed unenforceable, invalidated or circumvented, and if we do not obtain or maintain patent protection for the products, our business may be materially harmed.

The patent positions of biotechnology and pharmaceutical companies involve complex legal and factual questions and, therefore, validity and enforceability cannot be predicted with certainty. U.S. patents and patent applications also may be subject to interference proceedings, ex parte reexamination, inter partes review, or IPR, and post-grant review proceedings, derivation proceedings and supplemental examination and may be challenged in district courts. Patents granted in certain other countries may be subjected to opposition or comparable proceedings lodged in various national and regional patent offices. These proceedings could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application (so that, for example, they no longer cover competitors' products that are considered to infringe). In addition, such interference, re-examination, opposition, post-grant review, IPR, derivation proceedings, supplemental examination or revocation proceedings may be costly. We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that our proprietary technologies are covered by valid and enforceable patents or are effectively maintained as trade secrets. The degree of future protection for our products and proprietary rights is uncertain, and it cannot be guaranteed that:

- we will be able to successfully develop or commercialize our product before some or all of the relevant patents or regulatory exclusivity expire, or in countries where we do not have patent protection or exclusivity;
- we or our licensors were the first to make the inventions covered by each of the pending patent applications and patents;
- we or our licensors were the first to file patent applications for these inventions;
- others will not independently develop similar or alternative technologies or duplicate any of our technologies;
- any of our pending patent applications or those that we have licensed will result in issued patents;
- any of our patents or those we have licensed will be valid or enforceable;
- we will be able to license the patents or pending patent applications necessary or desirable to enforce or protect our patent rights on commercially reasonable terms or at all;
- any patents issued to us or our licensors or collaborators will provide a basis for protection of any existing or additional commercially viable products, will provide us with any competitive advantages or will not be successfully challenged by third parties;
- we will be able to develop additional proprietary technologies that are patentable; or
- the patents of others will not have an adverse effect on our business.

Changes in U.S. patent law or the patent law of other countries or jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. For example, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, made a number of significant changes to United States patent laws. These include provisions that affect the way patent applications are prosecuted and challenged at the USPTO and may also affect patent litigation. The USPTO has developed and continues to develop new regulations and procedures to govern administration of the Leahy-Smith Act. Accordingly, it remains unclear what impact the Leahy-Smith Act, subsequent rule-making, and judicial interpretation of the Leahy-Smith Act and regulations 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 an adverse effect on our business and financial condition. Moreover, future changes to the patent laws of the United States and foreign jurisdictions may adversely affect the term, scope, validity and enforceability of our or our licensors' patent rights. For example, a 2019 bill (Terminating the Extension of Rights Misappropriated Act, or TERM Act, H.R. 3199) in the United States Congress aimed to reduce the term of certain drug patents in order to ease generic entry and increase competition. Changing political priorities could potentially drive more such initiatives.

In addition, the U.S. Supreme Court and the U.S. Court of Appeals for the Federal Circuit have issued numerous precedential opinions in recent years narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of these decisions and legislative changes has created uncertainty with respect to the value of patents, once obtained. Depending on actions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce patents that we have licensed or that we might obtain in the future. Similarly, changes in patent law and regulations in other countries or jurisdictions or changes in the governmental bodies that enforce them or changes in how the relevant governmental authority enforces patent laws or regulations may weaken our ability to obtain new patents or to enforce patents that we have licensed or that we may obtain in the future. The U.S. federal government retains certain rights in inventions produced with its financial assistance under the Bayh-Dole Act. The federal government retains a ''nonexclusive, non-transferable, irrevocable, paid-up license'' for its own benefit. The Bayh-Dole Act also provides federal agencies with ''march-in rights.'' March-in rights allow the government, in specified circumstances, to require the contractor or successors in title to the patent to grant a ''nonexclusive, partially exclusive, or exclusive license'' to a ''responsible applicant or applicants.'' If the patent owner refuses to do so, the government may grant the license itself.

We enjoy only limited geographical protection with respect to certain patents.

Filing and prosecuting patent applications and defending patents covering product candidates in all countries throughout the world would be prohibitively expensive. Competitors may use our and our licensors’ technologies in jurisdictions where patent protection has not yet been obtained to develop their own products or may export infringing products to territories where enforcement rights are not as strong as in the United States or EU, or where enforcement rights do not exist. These products may compete with our product candidates, and our intellectual property rights may not be effective or sufficient to prevent such products from competing. Patent applications may be issued in some non-U.S. jurisdictions with different scope or they may be refused in certain jurisdictions, such as, for example. China, India, Brazil, which have different requirements for patentability.

Proceedings to enforce our patent rights in other jurisdictions, whether or not successful, could result in substantial costs and divert efforts and attention from other aspects of the business. They could also put our patents and patent applications at risk of being invalidated, denied or interpreted narrowly, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits or have damages or other remedies awarded to us, or such damages or other remedies may not be commercially meaningful. Accordingly, our intellectual property rights as enforced may be inadequate to obtain a significant commercial advantage and our efforts to protect our intellectual property rights may be unsuccessful or inadequate, which may adversely affect our ability to successfully commercialize our product candidates, and which may have a material adverse effect on our business, financial condition, results of operations and prospects. Furthermore, while we intend to protect our intellectual property rights in our expected significant markets, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our product candidates. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate, which may have an adverse effect on our ability to successfully commercialize our drug candidates in all of our expected, significant international markets.

Many countries also have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties or laws limiting the enforceability of patents against government agencies or government contractors under certain circumstances. In those countries, a patent owner may have limited recourse, which could materially diminish the value of such patents. If we or any of our licensors are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be adversely affected.

If intangible assets and goodwill that we record in connection with our acquisitions become impaired, we may have to take significant charges against earnings.

In connection with the accounting for our acquisitions, a significant value may be recognized in respect of intangible assets, including developed technology and customer relationships relating to the acquired product

lines, and goodwill. Under IFRS, we must assess, at least annually and potentially more frequently, whether the value of intangible assets and goodwill has been impaired. We expect to assess intangible assets and goodwill for impairment in the event of an impairment indicator. Any reduction or impairment of the value of intangible assets and goodwill will result in a charge against earnings, which could materially adversely affect our results of operations and shareholders' equity in future periods.

Our global operations subject us to significant tax risks.

We are subject to tax rules in the jurisdictions in which we operate. Changes in tax rates, tax relief and tax laws, changes in practice or interpretation of the law by the relevant tax authorities, increasing challenges by relevant tax authorities or any failure to manage tax risks adequately could result in increased charges, financial loss, penalties and reputational damage. Tax authorities may pursue additional taxes based on retroactive changes to tax laws which could result in a material restatement to our tax position. Any of these factors could have a negative impact on our business, financial condition, results of operations and prospects.

Risks Related to Government Regulation Compliance, Legal Matters, and Reputation

We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws, and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic markets. We can face criminal liability and other serious consequences for violations, which can harm our business.

We are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, antitrust and competition laws, various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls, the U.S. Foreign Corrupt Practices Act of 1977, or the FCPA, the United States domestic bribery statute contained in 18 U.S.C. § 201, the United States Travel Act, the USA PATRIOT Act, certain prohibitions under the Dutch Criminal Code (Wetboek van Strafrecht), the Dutch Economic Offences Act (Wet op Economische Delicten), the U.K. Bribery Act, and other state and national anti-bribery and anti-money laundering laws in the countries in which we conduct activities or countries that are otherwise relevant for our activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, contractors and other partners from authorizing, promising, offering, or providing, directly or indirectly, payments, or anything else of value to recipients in the public or private sector (in relation to an act or omission (to be or having been) by the recipient). We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, contractors, and other partners, even if we do not explicitly authorize or have actual knowledge of such activities, and we may participate in collaborations and relationships with third parties whose actions could potentially subject us to liability under the FCPA, the U.K. Bribery Act or local anti-corruption laws. We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United States and authorities in the EU, 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.

Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, disgorgement, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences.

If we fail to comply with United Kingdom, EU or U.S. privacy and data security laws and regulations, we may be subject to civil and criminal penalties and other liability.

We are also subject to laws and regulations covering data privacy and the protection of health-related and other personal information. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing focus on privacy and data protection issues which may affect our business, including recently enacted laws in many jurisdictions where we operate. The collection and use of personal data (including health data) in the EU is governed by the provisions of the GDPR. This regulation, which is wide-ranging in scope and includes extraterritoriality provisions that apply to certain entities located outside of the EU, imposes several requirements relating to the consent of the individuals to whom the personal

data relates, the information provided to the individuals, notification of personal data breaches to the competent national data protection authorities and the security and confidentiality of the personal data, and substantial fines for breaches of the data protection rules. The GDPR also imposes strict rules on the transfer of personal data out of the EU to other countries (including the United States). Failure to comply with the requirements of the GDPR and the related national data protection laws of the EU Member States and the United Kingdom may result in large fines and other administrative penalties: a failure to comply could result in fines up to the greater of 4% of annual worldwide turnover for the preceding financial year or €20 million, with infringements being grouped into tiers which trigger different maximum fine levels. Turnover in this context may include not only the entity in breach but also other group entities. Recent enforcement actions against multinational companies have resulted in significant fines.

Following the United Kingdom's formal departure from the EU on January 31, 2020, the United Kingdom adapted and implemented the GDPR into its national law, as a result of the United Kingdom's Data Protection Act 2018, or DPA. The DPA supplements the GDPR, and in particular sets out specific requirements related to the processing of ''special categories of personal data'', including personal data related to health, genetic information and personal data related to criminal offenses or convictions. The DPA also creates a number of criminal offenses (punishable by uncapped fines) for organizations and in certain cases their directors and officers. Since the United Kingdom left the EU and the transition period has expired, the United Kingdom became a "third country" for the purposes of EU data protection law.

A "third country" is a country other than the EU Member States and the three additional European Economic Area countries (Norway, Iceland and Liechtenstein) that have adopted a national law implementing the GDPR. Under the GDPR, personal data can only be transferred to third countries in compliance with specific conditions for cross-border data transfers. Unless an exemption applies, appropriate safeguards are required to enable transfers of personal data from the EU and EEA Member States. However, on June 28, 2021, the European Commission adopted an adequacy decision in relation to the United Kingdom. With this decision, the European Commission considers that personal data benefits from an essentially equivalent level of protection under UK law to that guaranteed under EU law, and thus allows personal data to flow freely from the EEA to the United Kingdom. This adequacy decision is however limited in time, and its renewal will depend on whether the United Kingdom continues to ensure an adequate level of data protection. As the United Kingdom is currently looking to reform its data protection regime, there is uncertainty as to whether the United Kingdom will be able to maintain its adequacy status in the future. Similarly, the European Commission adopted its adequacy decision for the EU-U.S. Data Privacy Framework on July 10, 2023, allowing the transfer of personal data from the EEA to U.S. companies participating in the EU-U.S. Data Privacy Framework.

Under the GDPR regulations, we are considered a controller of data processing and are subject to several legal obligations. In particular, we are obligated to place importance on collection and processing of special categories of personal data which, for our purposes, is data that reveals genetic data or data concerning health. While we have taken steps to comply with the GDPR and the DPA, we cannot assure you that our efforts to achieve and remain in compliance have been or will continue to be fully successful. The GDPR regulations and the DPA may impose additional responsibility and liability in relation to personal data that we process and we may be required to put in place additional mechanisms ensuring compliance with these or new data protection rules. This may be onerous and adversely affect our business, financial condition, results of operations and prospects.

In addition, we obtain patient health information from most healthcare providers that prescribe our products and research institutions with which we collaborate, and they are subject to privacy and security requirements under the Health Insurance Portability and Accountability Act of 1996, or HIPAA, in the United States. Although we are not directly subject to HIPAA other than with respect to providing certain employee benefits, we could potentially be subject to criminal penalties if we knowingly obtain or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA. There are also state laws on patient health information, such as the California Confidentiality of Medical Information Act, which we are more directly subject to. As more states consider implementing such laws, we may face an ever-expanding patchwork of data privacy regulations.

Failure to comply with healthcare laws and laws and regulations covering data privacy and the protection of health-related and other personal information could result in government enforcement actions, which could

include civil or criminal penalties, private litigation and adverse publicity and could negatively affect our business, financial condition, results of operations and prospects.

Our current and future relationships with healthcare professionals, customers and third-party payors are subject to applicable anti-kickback, fraud and abuse, privacy and security, transparency, and other healthcare laws and regulations, which could expose us to significant penalties, including criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

We are subject to healthcare statutory and regulatory requirements and enforcement by the U.S. federal government and the states and foreign governments in the jurisdictions in which we conduct our business. Third-party payors play a primary role in the approval of prescriptions for RUCONEST® and Joenja®, and we expect will do so for any product candidates for which we obtain marketing approval. Our current and future arrangements with third-party payors, healthcare practitioners and patients may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we research as well as market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations in the United States include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or paying remuneration, directly or indirectly, in cash or in-kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid; a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- the federal false claims laws, including the civil False Claims Act, impose criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government; in addition, the government may assert that a claim including items and services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- HIPAA imposes criminal and civil liability for, among other things, executing a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- the federal physician payment transparency requirements, sometimes referred to as the “Sunshine Act” under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or, collectively, the ACA, require certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children’s Health Insurance Program to report to Centers for Medicare & Medicaid Services, or CMS, information related to payments and other transfers of value to physicians, as defined by such law, and teaching hospitals and the ownership and investment interests of physicians and their immediate family members in such manufacturers. Beginning in 2022, applicable manufacturers also will be required to report such information regarding its relationships with physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists and certified nurse midwives during the previous year;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which also imposes obligations on certain covered entity healthcare providers, health plans, and healthcare clearinghouses as well as their business associates, and their subcontractors, that perform certain services involving the use or disclosure of individually identifiable health information, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- ACA, analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers;
- some state laws require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal

government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures;
- state and local laws that require the registration of pharmaceutical sales representatives;
- state and foreign laws also govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts;
- competition laws in the U.S. and globally that may govern our interactions with competitors, customers, distributors, and suppliers; and
- the FCPA prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations involve substantial costs. 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 it, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations, contractual damages, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs that we participate in, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We have certain price reporting obligations to the Medicaid Drug Rebate Program. Under the Medicaid Drug Rebate Program, we are required to pay a rebate to each state Medicaid program for RUCONEST® and Joenja®, and expect to do so for any new approved products. Those rebates are based on pricing data we have to report on a monthly and quarterly basis to CMS, the federal agency that administers the Medicaid Drug Rebate Program. These data include, among other things, the Average Manufacturing Price, or AMP, and the Best Price, or BP, which, in general, represents the lowest price available from the manufacturer to any entity in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts and other price concessions. On December 31, 2020, CMS promulgated a final rule that, among other things, changed the methodology for calculating and reporting of AMP and BP in order to encourage manufacturers and states to enter into value-based purchasing arrangements. We are liable for errors associated with our submission of pricing data and for any overcharging of government payors. For example, failure to submit monthly/quarterly AMP and BP data on a timely basis could result in a civil monetary penalty for each day the submission is late beyond the due date. Failure to make necessary disclosures and/or to identify overpayments could result in allegations against us under the Federal False Claims Act and other laws and regulations. Any required refunds to the U.S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition.

U.S. federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the 340B program in order for federal funds to be available for the manufacturer’s drugs under Medicaid and Medicare Part B. The 340B program requires participating manufacturers to agree to charge statutorily defined covered entities no more than the 340B “ceiling price” for the manufacturer’s covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low- income patients. The ACA expanded the list of covered entities to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, but exempts “orphan drugs” from the ceiling price requirements for these covered entities. The 340B ceiling price is calculated using a statutory formula based on the AMP and rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate Program, and in general, products subject to Medicaid price

reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. Any additional future changes to the definition of AMP and the Medicaid rebate amount under the ACA or other legislation or regulation could affect our 340B ceiling price calculations and negatively impact our results. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in an inpatient setting.

RUCONEST® has been approved by the FDA, the European Commission and certain other regulatory authorities for the treatment of HAE attacks. Regulatory approval is limited to the specific indication for which approval has been granted and, unless we seek regulatory approval for additional indications, we will be prohibited from marketing RUCONEST® for other indications. We may be subject to significant fines, penalties or injunctions if we are determined to have promoted or be promoting the use of RUCONEST® for unapproved or "off-label" uses, resulting in damage to our reputation and business.

RUCONEST® is approved by the FDA, the European Commission and certain other regulatory authorities for the treatment of HAE attacks, but is not currently approved for the treatment of other indications. Regulatory authorities strictly regulate the promotional claims that may be made about prescription products, and RUCONEST® may not be promoted for uses that are not approved, as reflected in its approved labeling. If we are not able to obtain regulatory approval for any desired future indications for our products and product candidates, our ability to effectively market and sell our products may be reduced and our business may be adversely affected.

While physicians may choose, in their independent medical judgment, to prescribe products for uses that are not described in the product's labeling and for uses that differ from those tested in clinical trials and approved by the regulatory authorities, we are prohibited from marketing and promoting the products for indications that are not specifically approved by the regulatory authorities. These "off-label" uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. Regulatory authorities in the United States and in other jurisdictions generally do not restrict or regulate the behavior of physicians in their choice of treatment within the practice of medicine. Regulatory authorities do, however, restrict communications by biotechnology or pharmaceutical companies on off-label use. If the FDA or another regulator determines that our promotional activities constitute promotion of an off-label use, it could request that we modify our promotional materials and subject us to regulatory or enforcement actions as well as actions by other agencies, including issuance of warning letters or untitled letters, suspension or withdrawal of an approved product from the market, mandatory or voluntary recalls, and could result in the imposition of significant criminal, civil, and administrative penalties such as civil fines, disgorgement of money, imprisonment, exclusion from participation in federal health care programs (e.g. Medicare and Medicaid), operating restrictions, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, injunctions or criminal prosecution, any of which could significantly harm our business.

Current and future healthcare legislative reform measures may have a material adverse effect on our business and results of operations.

In the United States and in some foreign jurisdictions, there have been, and likely will continue to be, a number of legislative and regulatory changes and proposed changes intended to broaden access to healthcare, improve the quality of healthcare and contain or lower the cost of healthcare. For example, the ACA substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacted the U.S. pharmaceutical industry. The ACA, among other things, subjects biological products to potential competition by lower-cost biosimilars, expands the types of entities eligible for the 340B drug discount program, 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, increases rebates owed by manufacturers under the Medicaid Drug Rebate Program and extends the rebate program to individuals enrolled in Medicaid managed care organizations, establishes annual fees and taxes on manufacturers of certain branded prescription drugs and creates a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018, or BBA, effective as of January 2019) point-of-sale discounts off negotiated prices of applicable 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.

Since its enactment, there have been numerous judicial, administrative, executive and legislative challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. In addition, the implementation of the ACA is ongoing, and the law appears likely to continue the downward pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs. Litigation and legislation related to the ACA are likely to continue, with unpredictable and uncertain results.

In addition, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several congressional inquiries and proposed legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient assistance programs and reform government program reimbursement methodologies for pharmaceutical and biological products. At the federal level, the previous administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that attempted to implement several of the administration's proposals, one of which has since been rescinded. As a result, the FDA released a final rule on September 24, 2020, effective November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. On January 5, 2024, the FDA authorized the state of Florida to import certain prescription drugs from Canada.

Further, on November 20, 2020, the U.S. Department of Health and Human Services, or HHS, finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Medicare Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Inflation Reduction Act of 2022, or IRA, until 2032.

The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has also been delayed by the IRA until January 1, 2032. Further, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, importation of drugs from Canada may materially and adversely affect the price we receive for any of our product candidates. It is unclear whether the Biden administration will work to reverse these measures or pursue similar policy initiatives. Additionally, on July 9, 2021, President Biden issued an executive order directing the FDA to, among other things, continue to clarify and improve the approval framework for generic drugs and identify and address any efforts to impede generic drug competition.

Additionally, on August 16, 2022, President Biden signed the IRA into law. The IRA, among other things, (i) directs HHS to negotiate the price of certain high-expenditure, single-source drugs and biologics covered under Medicare, and subject drug manufacturers to civil monetary penalties and a potential excise tax by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law, and (ii) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. The IRA permits HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. These provisions have taken effect progressively starting in fiscal year 2023, although they have been subject to legal challenges. It is currently unclear how the IRA will be effectuated but it is likely to have a significant impact on the pharmaceutical industry.

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 services by our partners or for our current or future drug

candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action in the United States. If we or any third parties we may engage are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, our drug candidates may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

Our employees and independent contractors, including principal investigators, consultants, any future commercial collaborators, service providers, and other vendors may engage in misconduct or other illegal activity.

Our employees and independent contractors, including principal investigators, consultants, commercial collaborators, service providers and other vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have an adverse effect on our results of operations.

Misconduct by these parties could include intentional, reckless and/or negligent conduct or other unauthorized activities that violate the laws and regulations of the FDA and other similar regulatory bodies, including those laws that require the reporting of true, complete and accurate information to such regulatory bodies; manufacturing standards; U.S. federal and state healthcare fraud and abuse laws, data privacy and security laws and other similar non-U.S. laws; or laws that require the true, complete and accurate reporting of financial information or data. 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 or misrepresentation of individually identifiable information, including, without limitation, information obtained in the course of clinical trials, the creation of fraudulent data in our preclinical studies or clinical trials, or illegal misappropriation of product, which could result in regulatory sanctions and cause serious harm to our reputation.

It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. In addition, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including, without limitation, the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgement, possible exclusion from participation in Medicare, Medicaid, and other U.S. federal healthcare programs or healthcare programs in other jurisdictions, integrity oversight and reporting obligations to resolve allegations of non-compliance, imprisonment, other sanctions, contractual damages, reputational harm, diminished profits and future earnings and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

There are material weaknesses in our internal control over financial reporting and if we are unable to remediate them, or if we identify additional material weaknesses in the future or otherwise fail to maintain an effective system of internal control, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect our business and stock price.

We have identified material weaknesses in our internal control over financial reporting across the principles for each component of the Committee of Sponsoring Organizations of the Treadway Commission, or COSO, framework (i.e., control environment, risk assessment, monitoring, information and communication and control activities) at the entity level and accordingly, across the business and IT processes of the Company. The material weaknesses that we identified relate to each of the five components of the COSO framework. See "Item 15 - Controls and Procedures" for additional information. If we are unable to remediate these material weaknesses, or if we identify additional material weaknesses in the future or otherwise fail to maintain an effective system of internal controls, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect our business and stock price.

In 2021, with the assistance of outside consultants, we established a compliance roadmap to work towards remediating material weaknesses in our internal control over financial reporting. In addition, during 2023, we established a control implementation plan and have been actively working on implementing key controls. As part of those efforts, we have, among other things, expanded hiring in our Finance and Internal Control functions and engaged an external party in testing the operating effectiveness of our internal control. We began the first round of operational effectiveness testing in the second half of 2023 and intend to undergo multiple rounds of operational effectiveness testing in 2024. However, we will not be able to fully remediate the material weaknesses until all of these steps have been completed and have been operating effectively for a sufficient period of time.

We have identified material weaknesses in our internal control over financial reporting across the principles for each component of the COSO framework since we became subject to the reporting requirements of the Exchange Act. We cannot assure you that we will be able to successfully remediate these material weaknesses or that other material weaknesses will not be discovered in the future. In addition, these efforts have caused us, and we expect will continue to cause us, to expend significant resources, including diverting management's attention from other business concerns.

We are required, pursuant to Section 404(a) of the Sarbanes-Oxley Act, to furnish a report by management on, among other things, the effectiveness of our internal control over financial reporting on an annual basis. This assessment includes disclosure of any material weaknesses identified by our management in our internal control over financial reporting. Our Management's Annual Report on Internal Control over Financial Reporting included in this Annual Report describes these material weaknesses and includes our conclusion that our internal controls were not effective as of the end of the period covered by this Annual Report. Additionally, an adverse opinion from our independent registered public accounting firm on our internal control over financial reporting is included in this Annual Report.

Our inability to conclude that we have effective internal control over financial reporting and out auditors' inability to provide us with an unqualified report on the effectiveness of our internal control over financial reporting, as required by Section 404, may (i) cause investors to lose confidence in the accuracy or completeness of our financial reports, (ii) cause the price of our ADSs or ordinary shares to decline and (iii) subject us to litigation, sanctions or investigations by regulatory authorities, including the SEC and Nasdaq. Failure to remediate the material weaknesses in our internal control over financial reporting could also restrict our future access to the capital markets. In addition, if we are unable to meet the requirements of Section 404, we may not be able to remain listed on Nasdaq.

Our business and operations may be negatively impacted by the failure, or perceived failure, of achieving environmental, social and governance, or ESG, objectives.

We continue to work towards operating our business in an environmentally responsible and socially inclusive manner. Stakeholders, including our stockholders and our employees, have increasingly focused on our ESG practices. If our ESG practices fail to meet these stakeholders' expectations and standards, there could be a material adverse effect on our reputation, business and, ultimately, our stock price.

Achieving our ESG goals requires long-term investments and broad, coordinated collaboration which may require us to incur additional costs or allocate additional resources towards monitoring, reporting, and implementing our ESG practices. Furthermore, we may fail to accurately assess our stakeholders' ESG priorities, as such priorities have evolved and will continue to evolve. Any failure or perceived failure to meet our ESG program priorities could result in a material adverse effect on our reputation, business, and stock price.

Risks Related to Financial Conditions, Market Environment and General Economic Trends

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets, including inflation and supply disruption.

A domestic or global financial crisis can cause extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn could result in a variety of risks to our business, including

weakened demand for our product candidates or an inability to purchase necessary supplies on acceptable terms, if at all. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payors or our collaborators. In addition, recent geopolitical tensions and conflicts, including the conflict in the Middle East and Ukraine, has had significant ramifications on global financial markets, which may adversely impact our ability to raise capital on favorable terms or at all. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Due to the international scope of our operations, fluctuations in exchange rates, particularly between the Euro and the U.S. dollar, may adversely affect us.

While we are headquartered in The Netherlands, we source materials, products and services from several countries outside the EU that are paid in local currencies. As a result of the commercialization of Joenja® in the United States and RUCONEST® in the United States and in other countries outside the EU, we will also receive payments and generate costs in U.S. dollars and other currencies. As a result, our business may be affected by fluctuations in foreign exchange rates between the Euro and the U.S. dollar, as well as other currencies.

Since the majority of our sales are invoiced and paid in U.S. dollars, and the majority of our costs and liabilities are valued in Euros, any change in the relevant exchange rate means a corresponding change in the Euro value of sales and a corresponding change in the loan balance in Euros. While we maintain U.S. dollar cash deposits, the functional currency of the Dutch Pharming entities is the Euro, so any change in the U.S. dollar-Euro exchange rate means a corresponding change in the Euro value of U.S. dollar cash deposits.

Adverse capital and credit market conditions may significantly affect the ability to meet liquidity needs, access to capital and cost of capital.

We utilize cash flow from operations to invest in our future projects. However, prolonged exposure to liquidity risk or inability to generate enough income for the currently contemplated projects, could lead to the inability to meet our financial obligations, which could increase the risk of insolvency.

Additionally, adverse developments in the capital and credit markets, for example as the result of rising interest rates globally, would affect our ability to finance our operations and could materially impact our results of operations.

Risks Related to the ADSs

As a "foreign private issuer," we are exempt from a number of rules under the U.S. securities laws and the Nasdaq Stock Market LLC, or Nasdaq, rules, and we are permitted to file less information with the SEC than are U.S. companies. In addition, we are permitted and follow certain home country corporate governance practices in lieu of certain Nasdaq requirements applicable to domestic issuers. This may make our American Depositary Shares, or ADSs, and ordinary shares less attractive to investors.

We are a "foreign private issuer," as defined in the rules and regulations of the SEC, and, consequently, we are not subject to all of the disclosure and governance requirements applicable to companies organized within the United States. For example, we are exempt from certain rules under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that regulate disclosure obligations and procedural requirements related to the solicitation of proxies, consents or authorizations applicable to a security registered under the Exchange Act. 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 a foreign private issuer traded on Euronext Amsterdam, we are permitted to follow certain home country corporate governance practices in lieu of certain requirements of the Nasdaq. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of the ADSs, are governed by Dutch law, including the provisions of the Dutch Corporate Governance Code, or the DCGC, and by our Amended and Restated Articles of Association, which may provide less protection than is afforded to investors under Nasdaq rules applicable to domestic issuers.

In particular, we follow Dutch law instead of Nasdaq practice in the following ways:

- We do not follow Nasdaq Rule 5620(c) regarding quorum requirements applicable to meetings of shareholders as long as we are not a domestic issuer and absent another mandatory obligation to such effect. Such quorum requirements are not required under Dutch law. In accordance with generally accepted business practice, our Amended and Restated Articles of Association provide alternative quorum requirements that are generally applicable to meetings of shareholders.
- We do not follow Nasdaq Rule 5605(b)(2), which requires that independent directors regularly meet in an executive session, where only independent directors are present. The independent directors may choose to meet in an executive session at their discretion.

As a result of the above, holders of the ADSs do not have the same protections afforded to shareholders of companies that are not foreign private issuers.

If securities or industry analysts do not publish research or reports about our business, or if they change their recommendations regarding the ADSs adversely, the price and/or trading volume of the ADSs could be affected.

The trading market for the ADSs representing our ordinary shares may be influenced by the research and reports that industry or securities analysts publish about us or our business. If one or more of the analysts who cover us or our industry downgrade the shares in a research report, the market price of the shares may decline and if one or more of these analysts ceases coverage of us or fails to publish reports on us regularly, we could lose visibility in the financial markets, which could cause the market price and/or trading volume of the shares to decline.

The price and trading volume of the ADSs and ordinary shares may be volatile, and purchasers of the ADSs or ordinary shares could incur substantial losses.

The market price of the ADSs is likely to be volatile and could decline significantly. The stock market in general, and the market for biotechnology and emerging pharmaceutical companies in particular, have experienced extreme volatility that has often been unrelated to the operating performance of particular

companies. The market price for the ADSs and ordinary shares may be influenced by a variety of factors, including:

- actual or anticipated variations in our financial condition and operating profit;
- actual or anticipated changes in our growth rate relative to our competitors;
- announcements of technological partnerships, innovations or new products by us or our competitors;
- the success of competitive products or technologies;
- changes in management and members of our board of directors;
- changes in financial estimates or recommendations by securities analysts;
- changes in the trading volume of the ADSs on the Nasdaq and of our ordinary shares on Euronext Amsterdam;
- sales of the ADSs or our ordinary shares by executive officers or future holders of our equity securities;
- announcements or expectations of additional debt or equity financing efforts;
- unanticipated losses or gains due to unexpected events, including events related to the success of our clinical trials or regulatory approvals;
- significant acquisitions or business combinations, strategic partnerships, joint ventures or capital commitments by or involving us or our competitors;
- changes in our accounting policies or practices;
- disputes or other developments related to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- changes in government regulations, including any changes that may affect pricing or reimbursement; and
- conditions in the financial markets or changes in general economic conditions.

These and other market and industry factors may cause the market price and demand for the ADSs and ordinary shares to fluctuate substantially.

Moreover, securities of life science companies, and stock markets in general, have from time to time experienced extreme price and volume fluctuations that may be unrelated or disproportional to the operational performance of any particular companies.

We will incur increased costs as a result of simultaneously having the ADSs listed in the United States and our ordinary shares admitted to trading on Euronext Amsterdam in The Netherlands, and our senior management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a company whose securities are publicly listed in the United States, we will incur significant legal, accounting and other expenses that we did not incur previously, even though our ordinary shares are admitting to trading on Euronext Amsterdam. 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, we expect that these rules and regulations may 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.

Further, being a U.S. listed company and a Dutch public company with ordinary shares admitted to trading on Euronext Amsterdam impacts the disclosure of information and requires compliance with two sets of applicable rules. From time to time, this may result in uncertainty regarding compliance matters and result in higher costs necessitated by legal analysis of dual legal regimes, ongoing revisions to disclosure and adherence to heightened governance practices. As a result of the enhanced disclosure requirements of the U.S. securities laws, business and financial information that we report is broadly disseminated and highly visible to investors, which we believe may increase the likelihood of threatened or actual litigation, including by competitors and other third parties, which could, even if unsuccessful, divert financial resources and the attention of our management and key employees from our operations.

Future sales of our ordinary shares or ADSs, or the perception that such sales may occur, could depress the prices of such ordinary shares or ADSs.

Sales of a substantial number of the ADSs in the public market, or the perception that these sales might occur, could depress the market price of the ADSs and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that such sales may have on the prevailing market price of our ADSs.

We are a Dutch public company with limited liability. The rights of our shareholders and ADS holders may be different from the rights of shareholders in companies governed by the laws of U.S. jurisdictions and may not protect investors in a similar fashion afforded by incorporation in a U.S. jurisdiction.

We are a public company (naamloze vennootschap) organized under the laws of The Netherlands. Our corporate affairs are governed by our Amended and Restated Articles of Association, the rules of our board of directors and by the laws governing companies incorporated in The Netherlands. However, there can be no assurance that Dutch law will not change in the future or that it will serve to protect investors in a similar fashion afforded under corporate law principles in the United States, which could adversely affect the rights of investors.

The rights of shareholders and ADS holders and the responsibilities of directors may be different from the rights and obligations of shareholders, ADS holders and directors in companies governed by the laws of U.S. jurisdictions. In the performance of their duties, our directors are required by Dutch law to consider the interests of our Company, its shareholders, its employees and other stakeholders, in all cases with due observation of the principles of reasonableness and fairness. It is possible that some of these parties will have interests that are different from, or in addition to, your interests as an ADS holder.

For more information on relevant provisions of Dutch corporation law and of our Amended and Restated Articles of Association, see “Description of Securities” included as Exhibit 2.1 to this Annual Report.

Provisions of our Amended and Restated Articles of Association or Dutch corporate law might deter acquisition bids for us that might be considered favorable and prevent, delay or frustrate any attempt to replace or remove the members of our board of directors.

Under Dutch law, various protective measures are possible and permissible within the boundaries set by Dutch law and Dutch case law.

Certain provisions of our Amended and Restated Articles of Association may make it more difficult or less attractive for a third party to acquire control of us or to effect a change in our board of directors. These provisions include: a provision that our directors are appointed on the basis of a binding nomination prepared by our board of directors which can only be overruled by a simple majority of votes cast representing at least one third of our issued share capital; a provision that our directors may only be removed by the general meeting of shareholders by a simple majority of votes cast representing at least one third of our issued share capital; and a requirement that certain matters, including an amendment of our Amended and Restated Articles of Association, may only be brought to our shareholders for a vote upon a proposal by our board of directors. Currently we have no such protective measures in place.

Shareholders and ADS holders may not be able to exercise preemptive rights and, as a result, may experience substantial dilution upon future issuances of ordinary shares.

In the event of an issuance of ordinary shares, subject to certain exceptions, each shareholder will have a pro rata preemptive right in proportion to the aggregate nominal value of the ordinary shares held by such holder. These preemptive rights may be restricted or excluded by a resolution of the general meeting or by another corporate body designated by the general meeting. For example, at our 2022 Annual General Meeting, our shareholders approved a proposal to exclude preemptive rights for up to 10% of our issued share capital for general corporate purposes and for up to 10% of our issued share capital for financing of mergers, acquisitions, and strategic alliances, each for a period of eighteen months. The issuance of additional equity securities in the absence of preemptive rights would cause existing shareholders to experience dilution of their interest in us.

We are not obligated to, and do not, comply with all best practice provisions of the Dutch Corporate Governance Code.

We are subject to the DCGC. The DCGC contains both principles and best practice provisions for boards of directors, shareholders and general meetings, auditors, disclosure, compliance and enforcement standards. As a Dutch company listed on a stock exchange, we are subject to the DCGC and are required to disclose in our annual board report to what we extent comply with the principles and best practice provisions of the DCGC, and where we do not (for example, because of a conflicting Nasdaq requirement or otherwise), we must state why and to what extent we deviate in our Annual Report. We do not comply with all best practice provisions of the DCGC. See "Description of Securities" included as Exhibit 2.1 to this Annual Report. This may affect your rights as a shareholder or ADS holder and you may not have the same level of protection as a shareholder or ADS holder in a Dutch company that fully complies with the DCGC.

We have never declared or paid dividends on our ordinary shares since our ordinary shares were listed on Euronext Amsterdam, and we do not anticipate paying dividends in the foreseeable future.

We have never declared or paid cash dividends on our ordinary shares since our ordinary shares were listed on Euronext Amsterdam. We intend to retain any earnings for use in our business and do not currently intend to pay dividends on our ordinary shares. Subject to restrictions under applicable law, any future determination to pay dividends or other distribution will be at the discretion of our board of directors and will depend upon a number of factors, including our results of operations, cash requirements, financial condition, future prospects, contractual restrictions, any future debt agreements, restrictions under applicable laws and other factors that our board of directors may deem relevant. We do not anticipate paying any cash dividends or other distributions on our ordinary shares in the foreseeable future. As a result, a return on any investment will only occur if the price of our ordinary shares or the ADSs increases.

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

While we do not anticipate paying any dividends or other distributions on our ordinary shares in the foreseeable future, if such a dividend or distribution is declared, the depositary for the ADSs has agreed to pay to you the cash dividends or other distributions it or the custodian receives on our ordinary shares or other deposited securities after deducting its fees and expenses, including any applicable withholding taxes. You will receive these distributions in proportion to the number of ordinary shares your ADSs represent. However, in accordance with the limitations set forth in the deposit agreement, it may be unlawful or impractical to make a distribution available to ADS holders. We have no obligation to take any other action to permit the distribution of the ADSs, ordinary shares, rights or anything else to holders of the ADSs. This means that you may not receive the distributions we make on our ordinary shares or any value from them if it is unlawful or impractical to make them available to you. These restrictions may have a material adverse effect on the value of your ADSs.

Dividends distributed by us on the ordinary shares or ADSs to certain related parties in low-taxed jurisdictions might in the future become subject to an additional Dutch withholding tax on dividends.

Under current Dutch tax law, dividends paid on ordinary shares or ADSs are in principle subject to Dutch dividend withholding tax at a rate of 15% under the Dutch Dividend Withholding Tax Act 1965 (Wet op de dividendbelasting 1965), unless a domestic or treaty exemption or reduction applies. Since January 1, 2024, the Dutch government has introduced an additional withholding tax on dividends paid to related entities in jurisdictions that have a corporate tax rate below 9% or to jurisdictions included on the EU's blacklist of non-cooperative jurisdictions and in certain abusive situations. The legislative proposal has been published by the Dutch government on March 24, 2021. Pursuant to the proposal, the conditional withholding tax on dividend payments will be an addition to the conditional withholding tax on interest and royalty payments pursuant to the Dutch Withholding Tax Act 2021 (Wet bronbelasting 2021). The rate will be as high as the highest Dutch corporate income tax rate (currently 25.8%) at the time of the dividend payment, which will be the statutory rate applicable to interest and royalty payments to related entities in jurisdictions that have a corporate tax rate below 9% or to jurisdictions included on the EU's blacklist of non-cooperative jurisdictions, to hybrid entities and in certain abusive situations. At the same time, the current Dutch dividend withholding tax regime is anticipated to remain in place. However, if the dividend withholding tax and the conditional withholding tax on dividends

cumulate, the conditional withholding tax will be reduced by the dividend withholding tax levied. As a result, if the shareholder being a related entity is established in a jurisdiction that has a corporate tax rate below 9% or in a jurisdiction included on the EU's blacklist of non-cooperative jurisdictions, the tax rate on dividends may rise from 15% to 25.8%.

ADS holders must act through the depositary to exercise their voting rights and, as a result, may be unable to exercise their voting rights on a timely basis.

We will not treat holders of the ADSs (rather than the ordinary shares underlying the ADSs) as shareholders, and they will not be able to exercise shareholder rights, except through our depositary and except that the ADS holders will have meeting rights to attend our general meetings. The depositary will be the holder of the ordinary shares underlying the ADSs, and ADS holders will be able to exercise voting rights with respect to the ordinary shares represented by the ADSs only in accordance with the deposit agreement relating to the ADSs. There are practical limitations on the ability of ADS holders to exercise their voting rights due to the additional procedural steps involved in communicating with these holders. For example, holders of our ordinary shares will be able to exercise their voting rights by either attending the shareholders meeting in person or voting by proxy. ADS holders, by comparison, will not receive any notice directly from us. Instead, in accordance with the deposit agreement, we will use commercially reasonable endeavors to provide at least 30 days' notice to the depositary of any such shareholders' meeting and details concerning the matters to be voted on in advance of the meeting date. If we so instruct, the depositary will distribute to ADS holders the notice of the meeting and a statement as to the manner in which voting instructions may be given, or deemed given in accordance with the deposit agreement by holders as soon as practicable after receiving notice from us of any such meeting. To exercise their voting rights, ADS holders must then instruct the depositary as to voting the ordinary shares represented by their ADSs. Due to these procedural steps involving the depositary, the process for exercising voting rights may take longer for ADS holders than for holders of ordinary shares. The ordinary shares represented by ADSs for which the depositary fails to receive timely voting instructions will not be voted.

The trading of our ordinary shares on Euronext Amsterdam and of our ADSs on the Nasdaq may adversely affect the liquidity and value of our ADSs.

Our ordinary shares are traded on Euronext Amsterdam, our ADSs have been approved for listing on the Nasdaq. We cannot predict the effect of this listing on the value of our ordinary shares and ADSs. However, these arrangements may dilute the liquidity of these securities in one or more markets and may adversely affect the development of an active trading market for the ADSs in the United States or the ordinary shares on Euronext Amsterdam. The price of our ADSs could also be adversely affected by trading in our ordinary shares on Euronext Amsterdam and the price of our ordinary shares traded on Euronext Amsterdam could be adversely affected by trading in ADSs on the Nasdaq. The speed by which ADSs can be exchanged for ordinary shares and subsequently traded on Euronext Amsterdam and vice versa might cause differences between the market price for an ADS and the market price for an ordinary share. Additionally, our ordinary shares are quoted in Euros on Euronext Amsterdam, and the ADSs are quoted in U.S. dollars on Nasdaq. Movements in the Euro-U.S. dollar exchange rate may adversely affect the U.S. dollar price of the ADSs on Nasdaq or the Euro price on Euronext Amsterdam. For example, if the Euro weakens against the U.S. dollar, the U.S. dollar price of the ADSs could decline, even if the price of our ordinary shares in Euros increases or remains unchanged. Investors might arbitrate between stock exchanges to exploit such differences, exacerbating potential volatility in our market price.

ADS holders may have difficulty in effecting service of process on our Company and certain directors or officers in the United States in enforcing U.S. judgments in The Netherlands or in enforcing U.S. securities laws in Dutch courts.

We are incorporated and located outside the United States and certain of our directors and officers are located outside of the United States. As a result, it may not be possible for ADS holders to effect service of process within the United States upon all such persons or our Company, or to obtain discovery of relevant documents and/or the testimony of witnesses. ADS holders based in the United States may also have difficulty enforcing in courts outside the United States judgments obtained in U.S. courts against our Company or our directors (including actions under the civil liability provisions of the U.S. securities laws). ADS holders may also have

difficulty enforcing liabilities under the U.S. securities laws in legal actions originally brought in jurisdictions located outside the United States.

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

The deposit agreement governing our ADSs provides that owners and holders of ADSs irrevocably waive the right to a trial by jury in any legal proceeding arising out of or relating to the deposit agreement or the ADSs, including claims under U.S. federal securities laws, against us or the depositary to the fullest extent permitted by applicable law. As the waiver relates to claims arising as a matter of contract in relation to the ADSs, we believe that, as a matter of construction of the clause, the waiver would likely to continue to apply to ADS holders who withdraw the ordinary shares represented by the ADSs from the ADS facility with respect to claims arising before the withdrawal, and the waiver would most likely not apply to ADS holders who subsequently withdraw the ordinary shares represented by ADSs from the ADS facility with respect to claims arising after the withdrawal. However, to our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the United States Supreme Court. If this jury trial waiver provision is prohibited by applicable law, an action could nevertheless proceed under the terms of the deposit agreement with a jury trial. Although we are not aware of a specific federal decision that addresses the enforceability of a jury trial waiver in the context of U.S. federal securities laws, it is our understanding that jury trial waivers are generally enforceable. Moreover, insofar as the deposit agreement is governed by the laws of the State of New York, New York laws similarly recognize the validity of jury trial waivers in appropriate circumstances. In determining whether to enforce a jury trial waiver provision, New York courts and federal courts will consider whether the visibility of the jury trial waiver provision within the agreement is sufficiently prominent such that a party has knowingly waived any right to trial by jury. We believe that this is the case with respect to the deposit agreement and the ADSs.

In addition, New York courts will not enforce a jury trial waiver provision in order to bar a viable set off or counterclaim of fraud or one which is based upon a creditor’s negligence in failing to liquidate collateral upon a guarantor’s demand, or in the case of an intentional tort claim (as opposed to a contract dispute). No condition, stipulation or provision of the deposit agreement or ADSs serves as a waiver by any holder or beneficial owner of ADSs or by us or the depositary of compliance with any provision of U.S. federal securities laws and the rules and regulations promulgated thereunder.

If any owner or holder of the ADSs, including purchasers of ADSs in secondary market transactions, brings a claim against us or the depositary in connection with matters arising under the deposit agreement or the ADSs, including claims under U.S. federal securities laws, such owner or holder may incur increased costs of bringing a claim and may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us or the depositary. Any legal suit, action or proceeding against or involving us brought by the depositary or any holder or beneficial owner of ADSs, arising out of or based upon the deposit agreement, the ADSs, the American Depositary Receipts, or ADRs, or the transactions contemplated therein or thereby, may be instituted only in any state or federal court in New York, New York. Any legal suit, action or proceeding against or involving the depositary brought by us, arising out of or based upon the deposit agreement, the ADSs, the ADRs or the transactions contemplated therein or thereby, may only be instituted in a state or federal court in New York, New York.

ADS holders may be subject to limitations on transfer of the ADSs.

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

We cannot assure you that we will not be a passive foreign investment company, or PFIC, for U.S. federal income tax purposes for any taxable year, which could result in adverse U.S. federal income tax consequences to holders of our ordinary shares or ADSs.