Pharvaris N.V.
(formerly Pharvaris B.V.)

Annual Report
for the fiscal year ended December 31, 2020

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BOARD REPORT

1 INTRODUCTION

1.1 Preparation

In this report, the terms "we", "us", "our" and "the Company" refer to Pharvaris N.V. (formally named Pharvaris B.V.) and, where appropriate, its subsidiaries.

During the fiscal year ended 31 December 2020, we were a private company with limited liability (*besloten vennootschap met beperkte aansprakelijkheid*) named Pharvaris B.V. On 5 February 2021, we were converted into a public limited liability company (*naamloze vennootschap*) and renamed Pharvaris N.V. in connection with the initial public offering of our ordinary shares and the admission to listing and trading of our ordinary shares on the NASDAQ Stock Market (the "**IPO**").

This report has been prepared by the Company's board (the "**Board**") pursuant to Section 2:391 of the Dutch Civil Code ("**DCC**") and also contains (i) the Company's statutory annual accounts within the meaning of Section 2:361(1) DCC and (ii) to the extent applicable, the information to be added pursuant to Section 2:392 DCC.

This report relates to the fiscal year ended December 31, 2020 and, unless explicitly stated otherwise, information presented in this report is as at December 31, 2020.

1.2 Forward-looking statements

This report contains certain statements that are or may be forward-looking statements with respect to us, our industry and our business that involve substantial risks and uncertainties. All statements other than statements of historical fact contained in this report, including statements regarding our future financial condition, results of operations and/or business achievements, including, without limitation, statements containing the words "believe," "anticipate," "expect," "estimate," "may," "could," "should," "would," "will," "intend" and similar expressions are forward-looking statements. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. Such forward-looking statements involve unknown risks, uncertainties and other factors which may cause our actual results, financial condition, performance or achievements, or industry results, to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements. Factors that might cause such a difference include, but are not limited to the expected timing, progress or success of our clinical development programs, especially for PHVS416 and PHVS719, which are in early-stage clinical trials; risks associated with the COVID-19 pandemic, which may adversely impact our business, preclinical studies and clinical trials, the timing of regulatory approvals and the value of our ordinary shares; the timing, costs and other limitations involved in obtaining regulatory approval for our product candidates PHVS416 and PHVS719 or any other product candidate that we may develop in the future; our ability to market, commercialize and achieve market acceptance for our product candidates PHVS416 and PHVS719 or any of our other product candidates that we may develop in the future, if approved; our

ability to establish commercial capabilities or enter into agreements with third parties to market, sell and distribute our product candidates; our dependence on third parties to perform critical activities related to the research, development and manufacturing of our product candidates; disruptions at the FDA and other government agencies; the expense, time and uncertainty involved in the development and consistent manufacturing and supply of our product candidates, some or all of which may never reach the regulatory approval stage; our ability to raise capital when needed and on acceptable terms; our ability to enter into any new licensing agreements or to maintain any licensing agreements with respect to our product candidates; our reliance on collaboration partners and licensees, whose actions we cannot control; the willingness of private insurers and other payors to provide reimbursement for our products; regulatory developments in the United States, the European Union and other jurisdictions; the outcome and timing of price negotiations with governmental authorities; our ability to compete in the pharmaceutical industry and with competitive generic products; our ability to protect our intellectual property and know-how and operate our business without infringing the intellectual property rights or regulatory exclusivity of others; side effects or adverse events associated with the use of our product candidates; our ability to defend against costly and damaging liability claims resulting from the testing of our product candidates in the clinic or, if, approved, any commercial sales; a loss of any of our key personnel; our estimates of market sizes and anticipated uses of our product candidates; our estimates of future performance; our estimates regarding anticipated operating losses, future revenues, expenses, capital requirements and our needs for additional financing; our ability to comply with existing or future laws and regulations in a cost-efficient manner; our ability to manage negative consequences from changes in applicable laws and regulations, including tax laws; our ability to successfully remediate the material weaknesses in our internal control over financial reporting and to maintain an effective system of internal control over financial reporting; our expectations regarding the time during which we will be an emerging growth company under the JOBS Act or a foreign private issuer; and changes in general market, political and economic conditions.

You should refer to the risk factors included in chapter 3.2 of this report for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

In addition, statements that "we believe" and other similar statements reflect our belief and opinions on the relevant subject. These statements are based upon information available to us as of the date of this report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

You should read this report and the documents that we reference in this report, completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

2 BUSINESS

2.1 History and development of the company

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapies for rare diseases with significant unmet need, initially focused on angioedema and other bradykinin-mediated diseases. Our first molecule, PHA121, is a novel, small-molecule bradykinin B2-receptor antagonist for the treatment of hereditary angioedema, or HAE. Bradykinin-B2-receptor inhibition is a clinically validated mechanism for the treatment of HAE, as demonstrated by icatibant, which is a bradykinin B2-receptor antagonist approved in Europe in 2008 and in the United States in 2011 (as FIRAZYR). We designed PHA121 to improve upon the therapeutic profile of existing therapies and, through oral delivery, to provide patients with quality of life and convenience that is superior to current standard-of-care HAE treatments, which are injectables. We believe PHA121 has the potential to provide a safe, effective and convenient option for both acute and prophylactic treatments of HAE, in the form of our PHVS416 on-demand rapid exposure product candidate, and for prophylaxis of HAE, in the form of our PHVS719 small daily dose extended-release product candidate. We believe that our product candidates may address a broader range of angioedema attacks than other available treatments since PHA121 blocks the actual signal that leads to angioedema (the interaction of bradykinin, or BK, with the bradykinin B2 receptor), rather than an upstream signal. By blocking the action of bradykinin, we can prevent its aberrant signaling regardless of the pathway that generates it. In our completed Phase 1 trials to-date, we have observed that PHA121 was orally bioavailable and well tolerated at all doses studied, with approximately dose-proportional exposure. We also have successfully demonstrated proof-of-mechanism through a clinical pharmacodynamics, or PD, assessment with the bradykinin challenge, which had been utilized as a validated surrogate assessment for dose selection in the icatibant development program. The data also allowed us to compare the projected therapeutic performance of PHA121 with that of icatibant, but we do not yet have data from the PHA121 Phase 2 study. We plan to efficiently progress PHA121 through clinical development for on-demand and prophylactic use with our on-demand product candidate, PHVS416, and extended-release product candidate, PHVS719, respectively. We commenced our RAPIDe-1 Phase 2 clinical trial of PHVS416 in February 2021 and expect to have Phase 2 data for the acute treatment of patients with HAE attacks in 2022. We are also planning to commence a Phase 2 clinical trial for prophylaxis in 2021 using twice-daily dosing of the PHVS416 soft capsules. Our primary objective with this trial is to assess the safety profile of PHVS416 dose regimens for prophylactic treatments in HAE patients. We are also planning to initiate a Phase 1 clinical trial with PHVS719 in 2021 before conducting the trial of PHVS719 in the prophylactic setting. We recently completed the 30-day review period with respect to our Investigational New Drug, or IND, application for developing PHVS416 in the prophylactic indication, and we remain on track to initiate the clinical trial for prophylaxis treatment in 2021.

Our legal and commercial name is Pharvaris N.V. In connection with our initial public offering in the first quarter of 2021, we converted the legal form of our company under Dutch law from a private company with limited liability (*besloten vennootschap met beperkte aansprakelijkheid*) to a public company with limited liability (*naamloze vennootschap*) and changed our name from Pharvaris B.V. to Pharvaris N.V. Pharvaris B.V. was founded in 2015 in Leiden, The Netherlands. Our principal executive offices are located in J.H. Oortweg 21, 2333 CH Leiden, The Netherlands, telephone: +31 (0) 71 203 6410.

The SEC maintains an Internet website that contains reports and other information about issuers,

like us, that file electronically with the SEC. The address of that website is www.sec.gov. Our website can be found at www.pharvaris.com. The information on our website is not incorporated by reference into this report, and you should not consider information contained on our website to be a part of report.

2.2 Overview

PHA121 is a novel, highly potent inhibitor and selective small molecule bradykinin B2-receptor antagonist and, to our knowledge, the only orally available bradykinin B2-receptor antagonist currently in development. PHA121 has been observed to be a potent inhibitor in vitro as assessed using human recombinant bradykinin B2 receptors (150 pM); ex vivo as studied against endogenous bradykinin B2 receptors in a human umbilical vein model (350 pM); and in vivo in the human bradykinin-challenge model (170 pM). Potency as used in this report refers to the amount of drug required to produce a pharmacological effect of given intensity and is not a measure of therapeutic efficacy. We do not yet have data from any PHA121 Phase 2 clinical trial to evaluate the potential therapeutic efficacy of PHA121 in HAE patients. PHA121 demonstrated 5000-fold selectivity for the bradykinin B2 receptor when compared to approximately 170 other molecular targets, including the bradykinin B1 receptor. We designed PHA121 as a new chemotype with properties compatible with oral delivery. We are developing PHA121 for the on-demand setting as PHVS416, which is delivered in a soft capsule designed to rapidly treat symptoms with a single dose. We are also developing PHA121 for the prophylactic setting as PHVS719, which is a small daily dose tablet with an extended-release formulation designed for the patient to achieve a steady-state plasma concentration within 72 hours.

In our Phase 1 clinical trials to-date, we have observed rapid exposure and predictable linear pharmacokinetics, or PK, with and without food. In addition, we observed PHA121 to be a potent antagonist of the bradykinin B2 receptor, in vitro and in vivo with healthy volunteers. In our models based on PK data from our Phase 1 clinical trial of PHA121 and published data for icatibant, both in the BK challenge assessment, PHA121 was shown to be consistently 25-fold more potent at inhibiting the effects of administered bradykinin than icatibant on a molar basis. We have not conducted a head-to-head comparison of icatibant to PHA121 in a clinical trial but have compared the published data for icatibant to data from our Phase 1 clinical trial of PHA121. While we believe this comparison to icatibant to be useful and appropriate, the value of this and other comparisons to icatibant in this report may be limited because they are not derived from a head-to-head trial and they are from trials that were conducted under different protocols at different sites and at different times. Without head-to-head data, we will be unable to make comparative claims for our product candidates, if approved.

HAE is a rare and potentially life-threatening genetic condition with symptoms that include episodes of debilitating and often painful swelling in the hands, feet, face (lips and tongue), gastrointestinal tract, urogenital region or airways. Attacks are unpredictable in frequency, location, timing, and severity, with multiple types of triggers. According to scientific publications, patients experience a median of 14 attacks per year, and half of patients experience a potentially life-threatening airway attack at least once in their lifetime. Airway attacks are particularly dangerous and can lead to asphyxiation. If left untreated, attacks can last multiple days and are commonly painful, leading to multiple sick days and even hospitalization. According to HAE International, as of October 2014, HAE affected from 1:50,000 to 1:10,000 individuals globally, or at least 6,600 patients in the U.S. and at least 8,900 patients in the EU.

Global sales of treatments for HAE achieved approximately $2 billion in 2018 and, according to public research reports, are forecast to grow at an approximately 9% compound annual growth rate

to $4.3 billion through 2027. Current approved products treat acute HAE attacks in an on-demand setting or seek to prevent or reduce future HAE attacks in a prophylactic setting. Each of these products generally works in one of the following ways: inhibiting the bradykinin B2 receptor, replacing the deficiency in C1-INH activity, or inhibiting plasma kallikrein. Currently most standard-of-care therapies are administered by injection, which patients can find challenging despite their efficacy because these therapies often result in painful injection-site reactions (leading some patients to delay treatment and risk attacks), are time consuming to receive (as some need to be administered in a clinic), and are difficult to carry and/or store. We believe HAE patients need alternatives that better meet their objectives for ease of disease treatment, disease control, and improved quality of life. We anticipate that there will be strong interest in safe and effective, orally delivered, small-molecule treatments that can match or improve upon the efficacy profile of existing therapies.

Based on results observed from our three completed and one ongoing clinical trials to-date, we believe our product candidates that contain PHA121 will demonstrate advantages and differentiation relative to currently approved HAE therapies and other oral therapies in clinical development. Namely, PHA121's bradykinin- B2-receptor-inhibition mechanism has a well-established clinical therapeutic profile in a currently approved product in the rapid treatment of acute HAE attacks. We have observed greater potency for PHA121 compared to icatibant in our early clinical trials, potentially resulting in both a smaller therapeutic dose and a longer duration of effect. We evaluated the PD and PK of PHA121 in a bradykinin-challenge model in healthy subjects. The bradykinin challenge was validated as a surrogate assessment for dose selection in the original development program for icatibant, as reviewed by the FDA and the EMA. The clinical dose of icatibant established with the bradykinin challenge has demonstrated successful treatment of HAE attacks in multiple randomized clinical trials and over 10 years of clinical experience. We conducted a proof-of-concept clinical trial testing the effects of BK in healthy volunteers in our bradykinin-challenge trial, where we evaluated the effect of PHA121 on cardiovascular parameters affected by bradykinin such as blood pressure, heart rate and cardiac output in healthy volunteers. We observed that PHA121 was more potent in blocking the effects of BK in humans than icatibant, when comparing the PHA121 results of the trial to published data on icatibant. The data from this trial allowed us to generate a PK/PD correlation model. Based on this model and published data on icatibant, we predict the duration of effect for a single oral dose of 12 mg PHA121 will exceed that of 30 mg of icatibant and a single oral dose of 22 mg PHA121 will cover the same duration of effect as two icatibant injections of 30 mg administered six hours apart. Furthermore, analysis based on the results from this trial suggest that therapeutic doses of PHA121 may be at least 20 times smaller than the doses required for oral kallikrein inhibitors in development. In addition, we believe that the observed PK profile of our compound demonstrates the potential of PHVS719 as a prophylactic treatment of HAE by achieving steady-state plasma concentrations within 72 hours. The BK-challenge data was generated in a Phase 1 clinical trial, and we do not yet have data from any PHA121 Phase 2 clinical trial to evaluate the potential efficacy of PHA121 in HAE patients. We have not conducted a head-to-head comparison of icatibant to PHA121 in a clinical trial but have compared the published data for icatibant to data from our Phase 1 clinical trial of PHA121. Potency as used in this report refers to the amount of drug required to produce a pharmacological effect of given intensity and is not a measure of therapeutic efficacy.

We have commenced a Phase 2 clinical trial, RAPIDe-1, that will evaluate angioedema symptom relief within four hours of different doses of PHVS416 or placebo while treating acute attacks of patients. We anticipate having Phase 2 data from RAPIDe-1 in 2022. Additional trials may be required by the FDA, EMA or other regulators even if we receive positive data from RAPIDe-1. We are also

planning to subsequently conduct a pivotal trial in the on-demand setting.

We are similarly planning two clinical trials in the prophylactic setting. In the first, subjects will be randomized to receive PHVS416 or placebo for three months. The primary objective is to assess the safety profile in HAE patients. For the second, we are planning a registration-directed trial with patients who will be randomized to receive PHVS719 or placebo to assess safety and efficacy in HAE patients. In addition, we also plan to run an open-label extension study in the prophylactic setting with both rollover and non-rollover subjects to collect longer duration safety data.

Differentiation of PHA121

We believe that PHA121, as the molecule underlying both PHVS416 and PHVS719, has the potential to be highly differentiated for both the on-demand and prophylactic settings with the key benefits below:

PHVS416. We believe that PHVS416, an on-demand, rapid exposure soft capsule, has potential to be highly differentiated for patients suffering from acute HAE attacks with the following benefits:

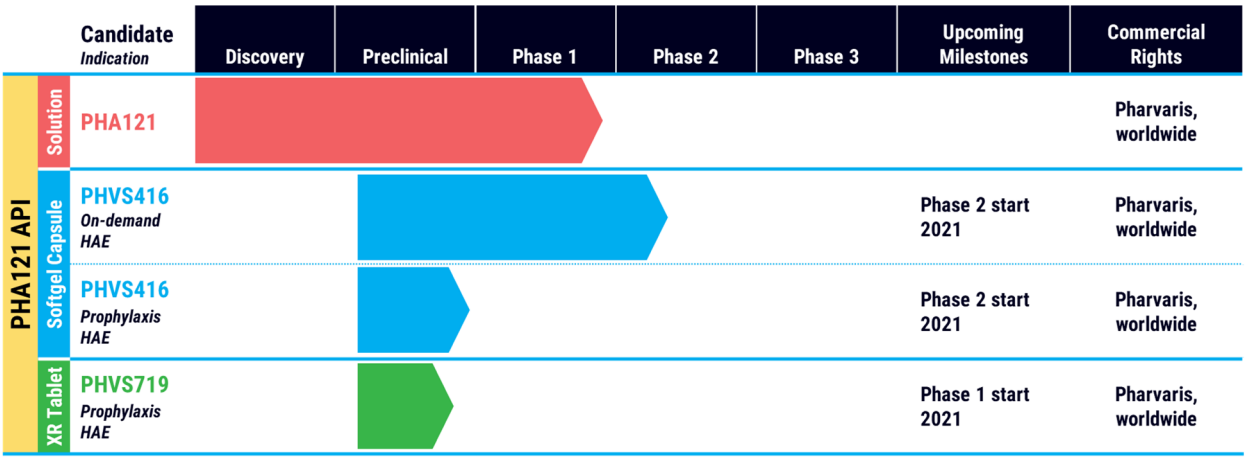
Complete Symptom Resolution	• Clinically validated mechanism of bradykinin-B2-receptor antagonism • Utilizing same surrogate assessment for dose selection as the development program for icatibant • More potent inhibitor than icatibant • Longer half-life than icatibant
Rapid Onset of Activity	• Exposure exceeds the anticipated threshold therapeutic plasma level (EC_{85}) in 15 minutes, with or without food
Potential Reduced Treatment Burden / Enhanced Patient Convenience	• No injection needed • Convenient oral formulation enables early treatment of acute HAE attacks • Capsule reduces treatment burden • Potential lowest dosage of any oral HAE on-demand treatment

PHVS719. We believe that PHVS719, a prophylactic extended-release tablet designed to be taken in small, daily doses, has potential to be highly differentiated for HAE patients with the following benefits:

Protection From Attacks	• Validated, proven mechanism to address all bradykinin, regardless of pathway
Ideal Release Profile for Prophylactic Use	• Reaches and maintains steady-state concentration within 72 hours • Appropriate pharmacokinetic profile with standard meals
Potential Reduced Treatment Burden / Enhanced Patient Convenience	• Convenient oral daily dosing with extended-release tablet • Twice-daily dosing with the potential for once a day • Potential lowest dosage of any oral HAE treatment; ease of administration

- Well tolerated throughout therapeutic ranges as demonstrated by multiple clinical trials to-date
- No injection needed

Our Pipeline



We plan to develop separate products for on-demand and prophylactic use, PHVS416 and PHVS719 respectively, with both products utilizing the same active ingredient, PHA121. PHVS416 will be a softgel capsule, and PHVS719 will be an extended-release tablet. We have commenced our RAPIDe-1 Phase 2 clinical trial of PHVS416 for on-demand use in 2021. We are also planning to commence a Phase 2 clinical trial for prophylaxis in 2021. In this trial, we plan to assess twice-daily dosing of PHVS416 softgel capsules for prophylactic use while we continue to advance the development of our extended-release formulation, PHVS719. We are also planning to initiate a Phase 1 clinical trial with PHVS719 in 2021 before conducting the trial of PHVS719 in the prophylactic setting. We recently completed the 30-day review period with respect to our IND application for developing PHVS416 in the prophylactic indication, and we remain on track to initiate the clinical trial for prophylaxis treatment in 2021.

Expansion of the Portfolio

Our ultimate goal is to expand our portfolio with additional programs addressing other BK-mediated diseases, building on our strategic strength and expertise in the bradykinin-B2-receptor pathway. Our approach is to identify additional disease areas and indications with strong scientific rationale, high unmet medical need, a defined target population and significant differentiation potential. We are actively pursuing new synthesis, medicinal chemistry and lead optimization to identify additional and/or follow-on product candidates. In collaboration and discussion with key opinion leaders, we are considering exploratory proof-of-concept studies to validate the potential of bradykinin-B2-receptor antagonism in new indications such as cardiovascular, allergy and immunology, neurological disease and others.

Our Strengths

Our Company is built upon the following strengths:

- Broad strength and expertise in the bradykinin-B2-receptor pathway. Members of the management team include an inventor of icatibant, the leadership team that developed icatibant through European approval, and a key member from the TAKHZYRO development team;
- PHA121 is an orally available product candidate with a clinically validated mechanism of action that addresses serious unmet medical need in HAE;
- PHA121 has demonstrated physicochemical properties suitable to formulations as both an on-demand product candidate, PHVS416, and a distinct prophylactic product candidate, PHVS719;
- PHA121, compared to icatibant, the currently approved bradykinin B2-receptor inhibitor, demonstrated superior preclinical potency in blocking bradykinin signaling at the bradykinin B2-receptor, and good oral bioavailability and a longer half-life in humans, which has resulted in longer duration of the BK-blocking pharmacodynamic effect in humans;
- We wholly own intellectual property – including allowed and in-process patent applications – covering PHA121 and additional molecules; and
- Our scientific experience allows us to leverage deep insight and experience in the bradykinin-B2-receptor pathway to expand our portfolio into other BK-mediated angioedema and BK-mediated diseases beyond angioedema.

Our Strategy

Our strategy is to develop and commercialize therapies that are superior to currently available treatment options and improve patient quality of life and convenience. Our initial approach for HAE and potential expansions into non-hereditary angioedema and other BK-mediated diseases is based upon extensive patient, physician and payer research to identify the key needs in the market. According to our analysis, oral therapy remains the highest unmet need for both on-demand and prophylactic use in HAE. More importantly, our research shows that patients are not willing to accept significantly reduced efficacy or safety with a switch to oral therapy, and so we place a high degree of emphasis on advancing product candidates that we believe can be comparable to or improve upon existing approved therapies in both safety and efficacy.

The key elements of our strategy include:

- *Continue to advance PHA121 through clinical development for on-demand treatment of HAE utilizing a fast-onset formulation, known as PHVS416.* We intend to develop and commercialize PHVS416 as a fast- acting, orally available, potent inhibitor and selective treatment for acute HAE. If considered appropriate by the FDA, we plan to pursue an expedited regulatory pathway that could allow us to more quickly provide patients with a potentially more effective oral therapy that is also more convenient.
- *Advance the development of PHA121 for prophylactic treatment of HAE utilizing an extended-release formulation, known as PHVS719*. We intend to advance PHVS719 through clinical development as an extended-release prophylactic treatment of HAE. We plan to leverage our clinical data and experience from the development of PHVS416 in the on-demand setting to expedite our efforts in the prophylactic setting. We expect the PK data from our Phase 2 trial

RAPIDe-1 of PHVS416 to help select and refine our prophylactic dose for the PHVS719 clinical trials.

- *Expand the range of bradykinin-mediated angioedema indications to which PHVS416 and PHVS719 can be applied*. In addition to Type 1 or Type 2 HAE, bradykinin is also an important mediator for other types of non-histaminergic angioedema, such as: non-histaminergic angioedema with normal C1-INH and acquired angioedema (AAE) due to C1-INH deficiency. Currently there are still no approved treatments for these angioedema patients who are unresponsive to conventional antihistamine/glucocorticoid treatment and have a high unmet medical need for effective therapies. Several clinical reports indicate that off-label use of icatibant has successfully treated acute attacks of non-histaminergic angioedema patients, which provides a strong rationale to expand the development PHVS416 and PHVS719 to address such a high unmet medical need.
- *Expand upon our expertise in the bradykinin-B2-receptor pathway*. We intend to leverage the strategic strengths, insight, and deep experience of our team in the bradykinin-B2-receptor pathway to identify additional disease areas and indications with strong scientific rationale, high unmet medical need, a defined target population and significant differentiation potential. As such, we will seek to develop follow-on product candidates that serve additional BK-mediated diseases beyond angioedema, such as cardiovascular, allergy and immunology, neurological disease or others.
- *Commercialize our product candidates*. We intend to retain economic and commercial ownership of our current product candidates. If approved, we expect to independently commercialize both PHVS416 and PHVS719 in the United States, Europe and certain other countries. As we advance towards regulatory approval for our product candidates, we will establish a focused commercialization and sales infrastructure suitable for HAE.

Hereditary Angioedema

Disease Overview

HAE is a rare and potentially life-threatening genetic condition. HAE is an autosomal dominant disease, meaning that a defect in only one copy of the gene leads to symptoms and that it occurs at similar rates in both males and females. It is mainly caused by one or more mutations (inherited or spontaneous) in the SERPING1 gene, which codes for the C1-esterase inhibitor protein C1-INH. Deficiency or malfunction of C1-INH leads to uncontrolled synthesis and activity of plasma kallikrein and unconstrained BK production. Excessive BK production is recognized to be the key mediator of symptoms in patients with HAE and manifests as edema attacks, most commonly in the limbs, face (lips and tongue), intestinal tract, urogenital region and airways. HAE patients with a deficiency in C1-INH activity are classified as Type 1 or Type 2. Type 1 is the most common form and results in low levels of circulating C1-INH, and Type 2 results in production of a low function protein. An additional form of HAE, called normal C1-INH HAE, can occur in patients with normal levels of C1-INH for a variety of reasons including mutations in genes for Factor XIIa, plasminogen, angiopoietin-1 or kininogen-1. Moreover, bradykinin-induced acute attacks of angioedema can occur idiopathically in individuals for which a hereditary cause has not yet been identified. Excessive amounts of BK can also be caused by increased circulation of estrogens, reduced C1-INH levels due to underlying diseases, reduced elimination of BK, or through use of medications such as angiotensin-converting enzyme, or ACE,

inhibitors and tissue plasminogen activator, or tPA.

Excessive BK generation and increased risks for edema attacks in HAE may occur during conditions associated with inflammation, infections, ischemia and allergic reactions. Attacks often lead to discomfort, pain and nausea but can become life-threatening in the case of airway obstruction, with a 30% risk of asphyxiation if the attack remains untreated. The number and severity of attacks vary highly between patients, and the most severely affected patients can experience attacks every few days. Attacks can occur spontaneously although they often are associated with anxiety, stress, minor trauma, surgery, or illnesses. Commonly, patients are alerted to an impending attack by prodromal symptoms which include rash, fatigue, and muscle aches. The severity of attacks is unpredictable and not related to their underlying frequency. Airway swelling is particularly dangerous and can lead to death by asphyxiation. Although rare, at least half of HAE patients have experienced a life-threatening airway swelling attack and airway attacks remain a major cause of mortality in HAE patients. Swelling typically develops over 24 hours and resolves within five days without treatment. Symptoms typically present in young children and may take 5-10 years or until early adolescence or young adulthood to be diagnosed. HAE affects 1:50,000 to 1:10,000 individuals globally, or at least 6,600 patients in the U.S. and at least 8,900 patients in the EU.

As a result of the lifelong nature of HAE and the challenges related to the use of many of the injected therapies, patient surveys consistently indicate an overwhelming desire for an oral therapy. We believe that a safe and effective oral agent has the potential to transform treatment for this disease. We also believe that opportunities exist for both acute and prophylactic treatments, and we intend to develop drug candidates for both on-demand and prophylactic use with the goal of providing patients with a set of oral options to prevent and treat their disease.

Current Treatments and Their Limitations

There are currently two treatment approaches to the management of HAE: acute (on-demand) treatment of attacks and prevention of attacks with short- or long-term prophylactic therapy.

- *On-Demand Treatment*: The currently approved products for treatment of acute HAE attacks are all injectable products and include C1-INH replacement products such as human plasma-derived C1-INH concentrates (BERINERT, CINRYZE, and CETOR) or recombinant human C1-INH (RUCONEST); the bradykinin-B2-receptor antagonist icatibant (FIRAZYR, and available as a generic product); and, the plasma kallikrein inhibitor ecallantide (KALBITOR), which has been known to cause allergic reactions including anaphylaxis and must be administered by a doctor or nurse in a healthcare setting. Human plasma-derived C1-INH concentrate products are isolated from donated human plasma and historically have been impacted by supply shortages. Subcutaneous, or s.c., icatibant is the only available bradykinin B2-receptor antagonist indicated for treatment of acute HAE attacks Type 1 or Type 2 with C1-INH deficiency. In acute HAE attacks, icatibant has been shown to provide a significantly faster onset of relief than placebo (2.0 h versus 19.8 h). Icatibant is recommended as a first-line treatment option for the treatment of acute HAE attacks in patients with HAE.
- *Prophylactic Treatment*: Currently approved prophylactic therapies for HAE include C1-INH replacement products, such as intravenously delivered CINRYZE and subcutaneously delivered HAEGARDA/ BERINERT 2000/3000 (both of which require twice-weekly injections); the monoclonal antibody plasma kallikrein inhibitor lanadelumab-flyo (TAKHZYRO); and the

recently approved small-molecule plasma kallikrein inhibitor berotralstat (ORLADEYO). Current treatment guidelines recommend against the use of the traditional oral medications for HAE, such as antifibrinolytics (tranexamic acid or epsilon aminocaproic acid) for HAE due to their limited efficacy. Attenuated androgens (e.g. danazol, stanozolol, and oxandrolone) are recommended only as second-line treatments for the prevention of HAE attacks, since there are numerous contraindications, therapeutic class adverse events, or AEs, and overall suboptimal control of HAE in many patients. The use of attenuated androgens is limited by numerous safety issues, including seborrhea, altered libido, depression, fatigue, menstrual abnormalities, and masculinization.

To our knowledge, three other angioedema-specific oral medications for acute, as well as prophylactic, use are in clinical development. All of these are kallikrein inhibitors. The angioedema-specific oral medications which, to our knowledge, are currently in clinical development, include:

Company	Asset	Mechanism of Action	Route of Administration	Trial Phase	Role in Therapy
KalVista	KVD900	Kallikrein inhibitor	Oral	2	Acute treatment
	KVD824	Kallikrein inhibitor	Oral	1	Prophylaxis
Attune	ATN-249	Kallikrein inhibitor	Oral	1	Prophylaxis

We believe that the properties and mechanism of PHA121 enable us to develop oral product candidates that will be generally more convenient for patients to take, without sacrificing efficacy for treatment or prevention of angioedema attacks. For example, the known oral kallikrein inhibitors tested in on-demand settings to date have utilized doses that are more than twenty-fold higher than the dose we predict for PHVS416, and have not yet demonstrated efficacy matching the approved injectable products. In the prophylactic setting, oral kallikrein inhibitors have not yet demonstrated efficacy similar to the approved injectable products, and have used or are projected to use doses much higher than we project for PHVS719.

Related indications to BK

In addition to Type 1 or Type 2 HAE, bradykinin is also an important mediator for other types of non-histaminergic angioedema, such as: non-histaminergic angioedema with normal C1-INH and acquired angioedema (AAE) due to C1-INH deficiency. Unlike HAE Types 1/2, for the other forms of non-histaminergic angioedema, an unclear pathophysiology and lack of consistent diagnostic criteria have limited the opportunity for the clinical investigation and new treatment development. Consequently, there are still no approved treatments for non-histaminergic angioedema patients with normal C1-INH or AAE due to C1-INH deficiency, who are unresponsive to conventional antihistamine/glucocorticoid treatment and have a high unmet medical need for effective modern therapies. Recently the clinical research for non-histaminergic angioedema has made significant progress. Similar to Type 1 or 2 HAE, the kinin pathway potentially plays a critical role in the underlying pathophysiology of non-histaminergic angioedema, for example, bradykinin has been shown to be elevated in plasma from non-histaminergic angioedema patients during acute attacks and several clinical

reports indicate that icatibant has successfully treated acute attacks in either non-histaminergic angioedema patients with normal C1-INH or AAE due to C1-INH deficiency patients. All these provide strong rationales to expand the development PHVS416 and PHVS719 to these types of BK-mediated angioedema and address the high unmet medical need.

PHA121

Overview

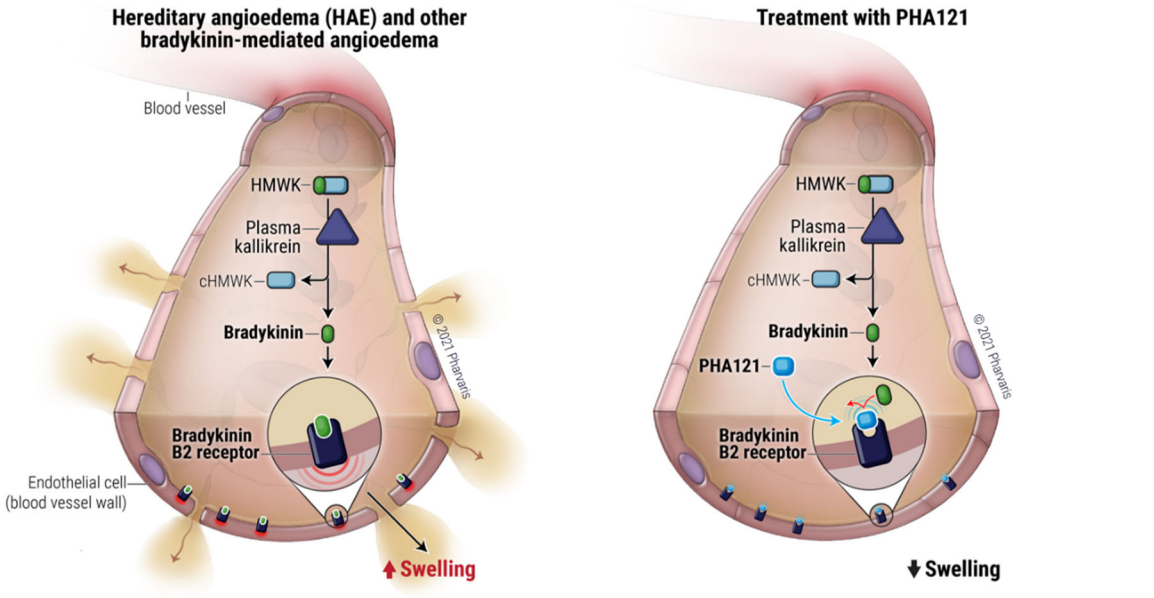
Since the 1990s, many companies have tried but failed to discover oral bradykinin-B2-receptor antagonists, as the bradykinin B2 receptor has proved to be a difficult target for the development of orally available antagonists. Historically, compounds targeting the bradykinin B2 receptor with adequate potency have had physicochemical properties inconsistent with oral bioavailability. The bradykinin B2 receptor is a G-protein coupled receptor (GPCR) that binds to the peptide bradykinin in an elongated fashion. It has been challenging to identify a small molecule that can bind in this pocket potently enough to compete with bradykinin while still being small enough with appropriate properties to demonstrate oral bioavailability. Starting with modeled structures of the bradykinin-binding pocket of the bradykinin B2 receptor, we designed and synthesized a novel lead series (a set of molecules with the potential to be further optimized). Through our lead optimization program, we synthesized over 600 compounds to select a small molecule that is designed to fit in the bradykinin- binding pocket at the bradykinin B2 receptor, preventing or halting its signaling activity, while also possessing desirable physicochemical properties and other profiling characteristics.

Bradykinin is the principal mediator of the signs and symptoms that represent acute HAE and other bradykinin-mediated angioedema attacks. Bradykinin is a potent and selective agonist of the bradykinin B2 receptor.

In HAE and other bradykinin-mediated angioedema, contact activation triggers increased activity of plasma kallikrein, resulting in excessive breakdown of high-molecular-weight kininogen (HMWK) and increased production of cleaved HMWK (cHMWK) and bradykinin.

Excessive bradykinin generation, as in HAE, promotes vascular permeability by activating the bradykinin B2 receptor, leading to plasma extravasation and subcutaneous or submucosal tissue swelling typical of an angioedema attack.

As the figure below illustrates, treatment with PHA121, an orally bioavailable low-molecular weight, potent, competitive and selective antagonist of the human bradykinin B2 receptor, is intended to block and prevent activation of the bradykinin B2 receptor by elevated bradykinin levels and prevent or halt the angioedema process, with reduced or resolved swelling as a consequence. PHA121 therefore has the therapeutic potential for both acute on-demand treatment and long-term prevention of attacks in patients with bradykinin- mediated angioedema.

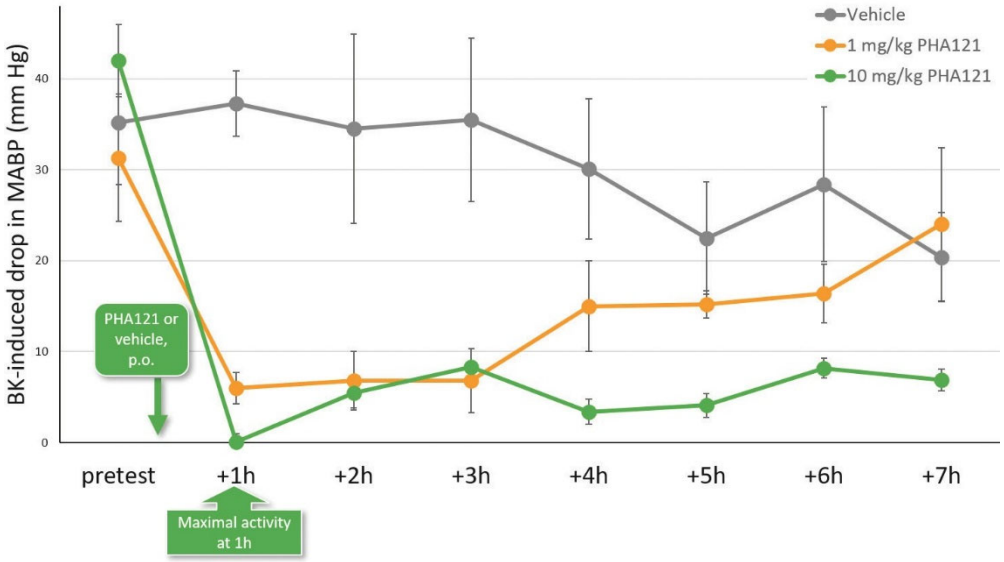


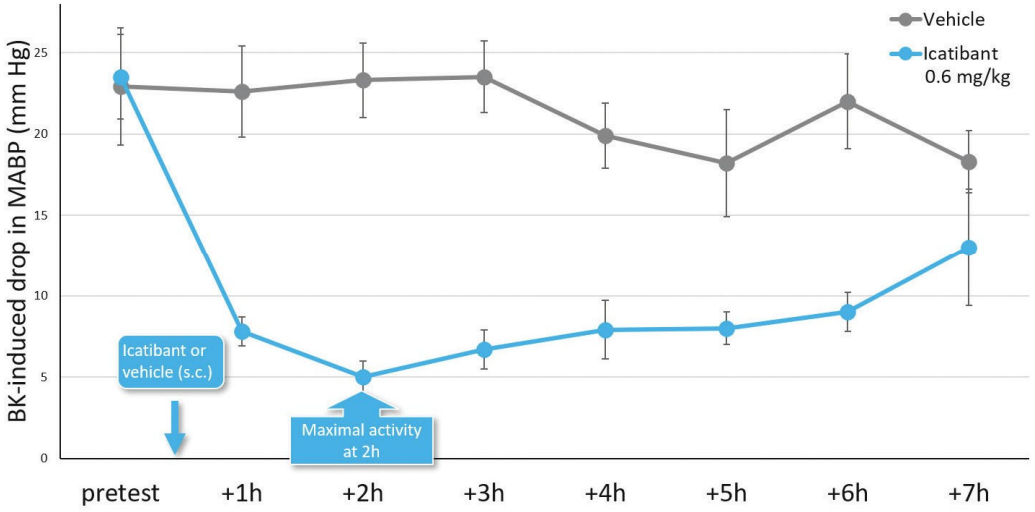
HMWK: high-molecular-weight kininogen; cHMWK: cleaved high-molecular-weight kininogen

PHA121 combines the preclinical selectivity of bradykinin-B2-receptor antagonism with oral bioavailability and extended exposure upon a single dose. PHA121 is being developed to become the first effective orally administered antagonist of BK activity with therapeutic potential for both acute on-demand treatment and long- term prevention of attacks in patients with HAE and other BK-mediated angioedema.

PHA121 is an orally bioavailable competitive antagonist of the bradykinin B2 receptor with high affinity and high antagonist potency. PHA121 has been observed to be a potent inhibitor in vitro as assessed using human recombinant bradykinin B2 receptors (150 pM); ex vivo as studied against endogenous bradykinin B2 receptors in a human umbilical vein model (350 pM); and in vivo in the human bradykinin-challenge model (170 pM). PHA121 demonstrated 5000-fold selectivity for the bradykinin B2 receptor when compared to approximately 170 other molecular targets, including the bradykinin B1 receptor. As shown in the graphs below depicting mean arterial blood pressure (MABP) in a bradykinin challenge study in monkeys (back-translated from human), PHA121 showed clear dose-dependent activity. While differences between human and monkey PK prevent direct extrapolation to human dose, PHA121 demonstrated longer duration and faster onset of activity than injected icatibant in the same study. We have not conducted a head-to-head comparison of icatibant to PHA121 in a clinical trial but have compared the published data for icatibant to data from our Phase 1 clinical trial of PHA121. While we believe this comparison to icatibant to be useful and appropriate, the value of this and other comparisons to icatibant in this report may be limited because they are not derived from a head-to-head trial and they are from trials that were conducted under different protocols at different sites and at different times. Without head-to-head data, we will be unable to make comparative claims for our product candidates, if approved.

BK-Challenge in Pre-Clinical Animal Model





In a published study conducted by the Company, a dose of 0.6mg/kg sc icatibant was used in monkeys, as PK data indicated that this dose would provide an exposure (Cmax 1,044 ng/ml, AUC 2,155 ng*h/ml, PHA0221-NC041) similar to the exposures seen in humans at a therapeutic dose of 30 mg sc (Cmax 979 ng/ml, AUC 2,191 ng*h/ml). The dose was found to effectively antagonize the BK challenge in monkeys up to six hours after dosing, similar to its duration of action in humans. The maximal effect of icatibant in this model was reached at the second measure time point, two hours after dosing. The vehicle in the icatibant study was saline.

PHA121 inhibited the BK-induced changes in MABP at all doses tested (0.1, 0.3, 1, 3 and 10 mg/kg given orally). The data show an early onset of activity, as the efficacy was already maximal at the first time point measured, one hour after oral dosing. This is a faster onset of action as compared to icatibant (0.6 mg/kg sc), which was maximally active on the BK-induced changes in MABP at two hours after dosing.

Preclinical Toxicology

We conducted secondary and safety pharmacology studies for PHA121 which did not reveal any safety concerns at exposure levels achieved or anticipated in conducted or planned clinical trials. In addition, PHA121 did not demonstrate any genotoxic or phototoxic potential. In repeat-dose general toxicity Good Laboratory Practices, or GLP studies in the rat and cynomolgus monkey of up to 3 months duration, and at doses up to the maximum tolerated in each species, no target organs of toxicity considered relevant to humans were observed. Functional assessment of male and female fertility is not yet complete but from repeat-dose GLP toxicity studies in rat and monkey, of up to 3 months duration, there are no organ weight or histopathological changes of concern in the reproductive tract of either gender. Furthermore, PHA121 has not demonstrated any adverse effects on embryo-fetal development in dose-range-finding embryo-fetal development studies in the humanized bradykinin- B2-receptor transgenic rat or in the rabbit.

Clinical Trial Program

Study	Short	Design	Status
Phase 1			
C001	Single ascending dose (SAD) and BK challenge / SAD-proof of mechanism (POM)	Randomized, double-blind, placebo-controlled, single ascending dose to assess safety and proof-of-mechanism through BK-challenge	Completed
C002	SAD extension	Randomized, double-blind, placebo-controlled, single ascending dose to assess safety	Completed
C003	Absorption, metabolism and excretion (mass balance)	Open-label, single dose ^{14}C-PHA121 to characterize the absorption, metabolism and excretion	Commenced (2021)
C004	Drug-drug interaction (DDI)—CYP3A4 inhibitor (itraconazole) interaction	Open-label, single-sequence, crossover DDI study	Completed
C005	DDI—CYP interaction (cocktail)	Open-label, single-sequence, crossover DDI study	Commenced (2021)
C006	Multiple ascending dose (MAD)	Randomized, double-blind, placebo-controlled, multiple ascending dose to assess safety and different doses	Completed (2021)
Phase 2			
C201 RAPIDe-1	PHVS416 on-demand	Phase 2, randomized, double blind, placebo-controlled, dose ranging study to assess safety and efficacy	Commenced (2021)

C301	PHVS416	Phase 2, randomized, double blind, placebo-controlled, dose ranging	Planned

PHA121-C001 (SAD and BK challenge / SAD-POM)

PHA121-C001 was a randomized, double-blind, placebo-controlled, single ascending dose and proof-of-mechanism study to examine the safety, tolerability, PK and PD of orally administered PHA121 in healthy subjects. A total of 52 subjects received single ascending oral doses of PHA121 up to 22 mg. The 16 remaining subjects received placebo. No adverse event, or AE, was reported as serious, no premature withdrawals due to AEs occurred and no severe AEs were reported. In addition, no clinically relevant fluctuations of blood pressure and no orthostatic hypotension linked to PHA121 groups occurred. The overall incidence of AEs was similar between the placebo and PHA121. Treatment-related AEs were reported for three subjects who received PHA121 (12 or 22 mg), all within the gastrointestinal system and of mild severity: upper abdominal pain, vomiting, and nausea. There were no apparent trends or dose-related changes in hematology, clinical chemistry, vital signs, or ECG.

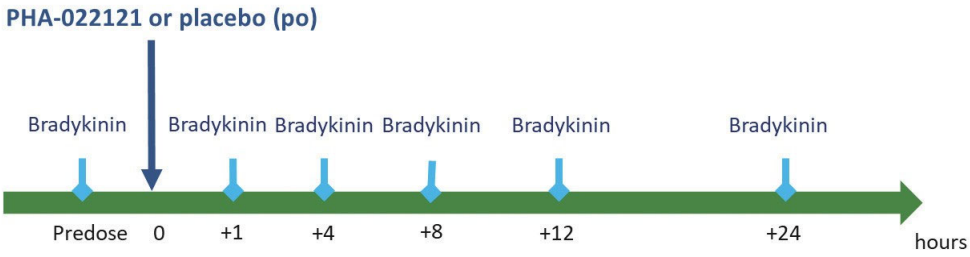
Pharmacokinetics Analysis

Dose proportional PK was observed after single oral administration under fasting condition of PHA121 in the dose range of 1 mg to 22 mg for Cmax, AUClast and AUCinf. Median tmax in the dose range of 1 mg to 22 mg was between 0.50 hour and 1.00 hour, with comparable ranges of individual values (ranging between 0.25 hour and 1.02 hours). Less than 1% of the dose was excreted unchanged in urine within 72 hours after administration.

Dose (mg)	**C_{max} (ng/mL)**	**$C_{0.25h}$ (ng/mL)**	**C_{12h} (ng/mL)**	**T_{max} (h)**	**$t_{1/2}$ (h)**
1	11	6	0.5	0.5	3.5
2	20	13	0.8	0.75	4.3
4.5	33	13	1.9	1.0	4.4
12	97	60	5.6	0.5	4.3
22	213	143	8.3	0.75	5.6
22 (high-fat, high cholesterol)	145	48	19.6	3.0	5.3

In this study, a high-calorie, high-fat meal reduced peak exposure and slightly increased overall exposure of PHA121: after a 22 mg dose, the mean Cmax of PHA121 was lower (~32%) while AUCinf was higher (~ 42%) when PHA121 was administered after a high calorie, high-fat breakfast (fed conditions) compared to administration under fasted conditions. While the median Tmax of PHA121 was delayed by approximately two hours after administration under fed conditions, the plasma concentration for PHA121 still reached the projected therapeutic levels (EC85, as determined in the bradykinin challenge described below) within 15 minutes. As shown in the table, the concentration of PHA121 twelve hours post-dosing at 12 mg or 22 mg remained above projected therapeutic levels under both fed and fasted conditions.

Bradykinin Challenge Study



In addition, we also evaluated the PD of PHA121 in a bradykinin challenge model, which was designed to demonstrate PHA121-mediated inhibition of the drop in blood pressure and increase in heart rate resulting from injection of a bradykinin bolus in healthy subjects. The bradykinin challenge is administered at specific intervals after the PHA121 or placebo dose, and the inhibition of bradykinin-induced hemodynamic effects is a validated surrogate assessment that was used to select the dose in the original development program for icatibant, as reviewed by FDA and EMA. The clinical dose of icatibant established with the bradykinin challenge has demonstrated successful resolution of HAE attacks in randomized clinical trials and over 10 years of data post- approval.

In the bradykinin challenge, we assessed the inhibition of bradykinin effects at single doses of 12 and 22 mg PHA121. Bradykinin was injected intravenously before PHA121 to calibrate each subject's response, and then at 1, 4, 8, 12 and 24 hours after dosing with PHA121. We monitored cardiovascular responses at each time point (see figure above). At the same time, blood samples were drawn for PK assessment. Bradykinin injection induced a short-term change in mean arterial blood pressure, or MABP, heart rate, or HR, and cardiac output. In the presence of PHA121, this cardiovascular response was dampened to an extent depending on the concentration of PHA121.

We conducted a PK/PD analysis using the same approach as used by FDA in their evaluation of icatibant. The composite EC50 and EC85 values estimated from the combination of each PD response associated with the BK challenge are provided in the table below. PHA121 demonstrated higher PD potency based on plasma concentrations (roughly four-fold) than icatibant relative to published data for icatibant. Adjusting for the differences between molecular weight and plasma protein binding, we found that PHA121 is 24-fold more potent (170 pM) in the bradykinin challenge than icatibant (4.1 nM) on a molecule-by-molecule basis, consistent with our preclinical in vitro measurements.

Composite average	**PHA121**	**Icatibant**
EC_{50} (ng/mL)	2.4	9.5
EC_{85} (ng/mL)	13.8	53.8

EC_{50}: concentration at which compound induces a response half of its maximum possible response;
EC_{85}: concentration at which a compound induces 85% of its maximum response.

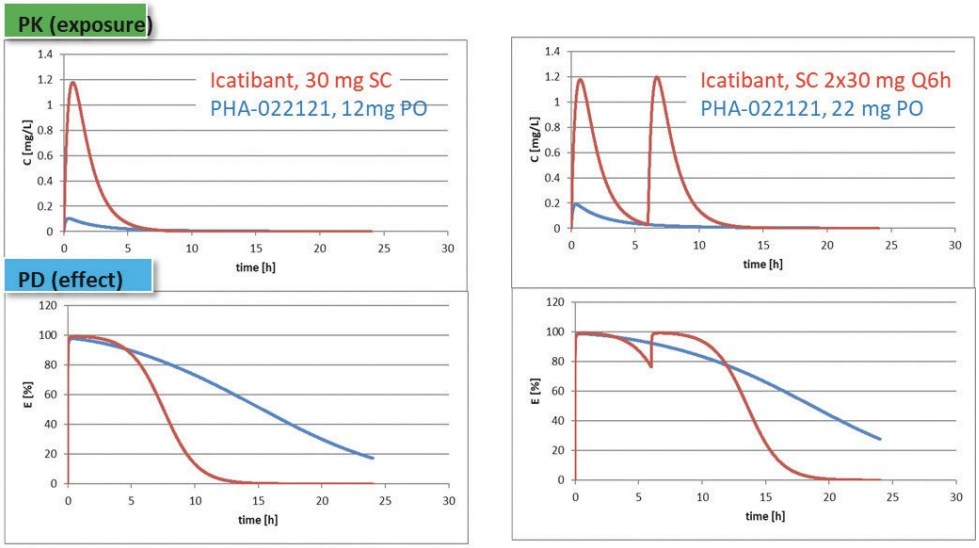
The data also allowed us to compare the projected therapeutic performance of PHA121 with that of icatibant, but we do not yet have data from the PHA121 Phase 2 study. In addition, we have not conducted a head-to-head comparison of icatibant to PHA121 in a clinical trial but have compared the published data for icatibant to data from our Phase 1 clinical trial of PHA121. While we believe this comparison to icatibant to be useful and appropriate, the value of this and other comparisons to icatibant

in this report may be limited because they are not derived from a head-to-head trial and they are from trials that were conducted under different protocols at different sites and at different times. Without head-to-head data, we will be unable to make comparative claims for our product candidates, if approved. Clinical trials have shown for icatibant that the therapeutic response to an acute HAE attack wanes approximately 6 hours after dosing, coinciding with the drop in icatibant concentration below therapeutic levels due to the short half-life (1.4 hours) of the drug. More precisely, it was shown that icatibant plasma concentrations with a 75% probability to be above EC50 and a 50% probability to be above EC85 correlate with therapeutic efficacy. Applying these criteria as exposure targets for PHA121 leads us to project that due to PHA121's longer half-life, we believe PHA121 will stay above these therapeutic targets for much longer than icatibant. The 12 mg dose of PHA121 showed rapid absorption and then stayed above EC50 for 10-12 hours and above the EC85 for 7 hours, suggesting that this dose may be at least as effective as a 30 mg s.c. injection of icatibant. A 30 mg s.c. icatibant dose has been documented to effectively treat 93% of acute HAE attacks (Icatibant Outcome Survey, or IOS, study reference).

The table below compares 30 mg of icatibant to 12 mg and 22 mg of PHA121 based on BK-challenge modeling and simulation.

Response	Icatibant 30 mg	PHA121 12 mg (oral)	PHA121 22 mg (oral)
	Time (h) plasma level above EC50 at a 75% confidence level		
Diastolic blood pressure (DBP)	6	11.5	14
MABP.....	6	12	15.5
Heart rate	6.5	10	13
	Time (h) plasma level above EC85 at a 50% confidence level		
DBP	5.5	7.5	10
MABP.....	5.5	7	10
Heart rate	5.5	6.5	9.5

The chart below shows the simulation of PK and PD resulting from single (left) or double (right) doses of icatibant as compared to single doses of PHA121 at 12 mg (left) or 22 mg (right), using a non-linear mixed-effect model built from published data of icatibant and our bradykinin challenge study. As shown in the bottom row, the modeled PD effect of PHA121 surpasses that of icatibant at less than half the dose, and equals two 30 mg injections of icatibant with a single oral dose of 22 mg. As demonstrated in a post-commercialization observational study (IOS study reference), a single dose of icatibant was shown to treat 93% of attacks and two doses treated 99% of over 5,000 attacks in the 10 years survey.



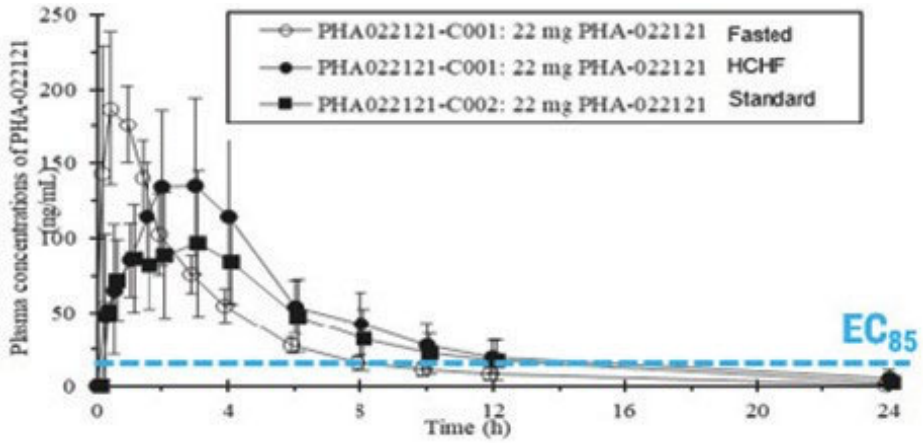
In conclusion, PHA121 was well tolerated when administered orally at the doses tested without any dose- limiting toxicity. PHA121 was rapidly absorbed in either fasting or fed conditions and showed dose proportional PK for PHA121. The BK challenge demonstrated that PHA121 potently blocks the effects of bradykinin-induced hemodynamic changes and provided the robust rationale for dose selection in future on-demand and prophylactic HAE trials.

PHA121-C002 (SAD extension)

PHA121-C002 was a randomized, double-blind, placebo-controlled, single ascending dose extension trial designed to examine the safety, tolerability, and PK of single ascending oral doses of 22, 33, and 50 mg of PHA121 after a standard caloric meal and 40 mg in fasting conditions. A total of 32 subjects received either PHA121, with respect to 24 subjects, or placebo, with respect to 8 subjects.

The trial results showed that PHA121 was well tolerated at doses up to 40 mg under fasting and 50 mg under fed conditions. There were no SAEs reported. Treatment-related AEs that were reported as possibly related to PHA121 were mild nausea (22 mg) (one subject), mild headache (50 mg) (one subject), and moderate headache associated with vomiting (50 mg) (one subject). There were no clinically significant changes in vital signs, laboratory or ECG parameters.

Over the investigated dose range from 22 to 50 mg (factor 2.27 increase) after a standardized breakfast, PHA121 showed dose-proportional PK with a 2.4-fold increase for mean Cmax and AUC0-24h. Administration of PHA121 after a standardized breakfast resulted in 40-50% decrease in Cmax without a change in AUCinf as compared to administration under fasting conditions. As a result, C12h and C24h plasma concentration for PHA121 were higher under fed conditions. These observations support the potential use of this formulation for initial studies in a prophylactic setting by dosing with food.



	22 mg of PHA121 Fasted	22 mg of PHA121 HCHF	22 mg of PHA121 Standard Meal
C12h' ng/mL.....	8.3	19.6	17.3
C24h' ng/mL.....	1.1	5.4	2.5
Cmax' ng/mL.....	213	145	115
AUC0-24h' ng.h/mL....	671	966	750
Tmax' h	0.25-1.02	2.00-3.00	0.50-4.00
t1/2' h.....	5.6	5.3	4.3

PHA121-C004 (DDI-CYP3A4 inhibitor, itraconazole, interaction)

Cytochrome P450 3A4 (CYP3A4) plays an important role in the metabolism of PHA121. PHA121-C004 was designed as an open-label, single sequence crossover drug-drug interaction trial to evaluate the effect of multiple doses of itraconazole, a potent CYP3A4 inhibitor, at steady-state on the PK of a single dose of PHA121 in healthy subjects. The primary objective of this study was to determine the effect of multiple doses of the strong CYP3A4 inhibitor itraconazole on the PK of PHA121 in healthy adult subjects. The secondary objective of this study was to evaluate the safety and tolerability of PHA121 alone and in combination with multiple doses of the CYP3A4 inhibitor itraconazole in healthy adult subjects. The study has been completed in 13 subjects and PHA121 was well tolerated with no drug-related adverse events reported. Preliminary analyses show that the exposure of PHA121 increased when co-administered with itraconazole, as expected from in vitro data showing that PHA121 is a substrate of CYP3A4. Other potential drug-drug interactions will be further assessed by the PHA121-C005 cocktail interaction study and in in vitro assays recommended by FDA guidance.

PHA121-C006 (MAD)

PHA121-C006 was a randomized, double-blind, placebo-controlled, multiple ascending dose trial to examine the safety, tolerability and PK of PHA121 in healthy subjects, which demonstrated PHA121's pharmacokinetics and tolerability. The trial included 38 subjects and four cohorts, ranging from 12 to 50 mg, of healthy subjects who were studied sequentially. Within each cohort, eight subjects received PHA121 and two subjects received placebo, except for the final cohort with six subjects receiving PHA121 and two subjects receiving placebo. The trial evaluated multiple ascending doses of

twice daily for 10 days to establish safety and tolerability and to assess the PK characteristics of PHA121 after standard caloric meals. PHA121 was supplied as an oral solution.

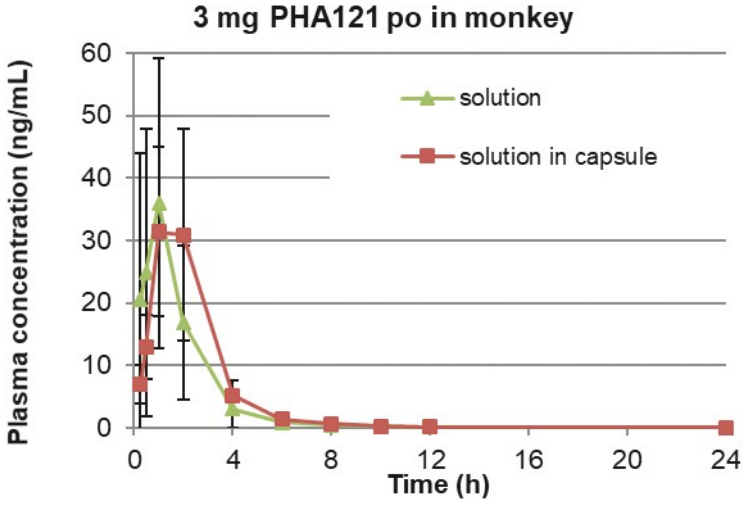
The study showed PHA121 was well tolerated at all doses studied (including up to the highest dose of 50 mg twice daily (BID)), with approximately dose-proportional exposure. During the study, there have been no SAEs or severe treatment-emergent adverse events, or TEAEs, reported. All reported TEAEs were mild in intensity and resolved completely. There were no clear differences between the different dosing regimens vs. placebo with respect to the total TEAEs and the frequency of TEAEs reported for the different system organ classes. Lab safety, vital signs, and ECG parameters remained well within normal limits in all subjects. The pharmacokinetic profile suggests that therapeutic drug levels of PHA121 were achieved in day 1 and steady-state plasma concentrations were reached within 72 hours.

Future Development Path

We intend to develop PHA121 for on-demand and prophylactic indications in parallel using two different product formulations, with clinical trials in the on-demand setting commencing first in order to provide critical data for further development for the prophylaxis indication.

RAPIDe-1 On-Demand

The availability of an immediate-release soft-capsule formulation, PHVS416, provides a good pharma- cokinetic profile for on-demand treatment: rapid oral absorption independent of fed status resulting in almost immediate onset of action with longer expected duration of efficacy than subcutaneous injections of icatibant. We have observed in preclinical animal studies that the PHVS416 soft capsule provides the same pharmacokinetic profile as the solution formulation we used in Phase 1 trials.



In February 2021, we commenced an on-demand Phase 2 clinical trial in HAE patients, RAPIDe-1, that will evaluate angioedema symptom relief within four hours using different doses of PHVS416 versus placebo while treating acute attacks of patients with HAE Types 1 and 2. Eligible patients are randomized to one of three single doses of active and placebo. The primary endpoint will be the change in composite visual analogue scale, or composite VAS, a measure of symptom relief, at

four hours post-dose. Composite and individual VAS, mean symptom complex severity, or MSCS, and treatment outcome score, or TOS, will be assessed up to 48-hours post-dose. We expect data in 2022.

Prophylaxis Trials

Currently there is no bradykinin B2-receptor antagonist available for HAE prophylaxis. Icatibant has a very short half-life and would require multiple injections each day, making it generally unsuitable for prophylactic use, especially with injection site pain reported for most patients.

Unlike on-demand use, prophylaxis requires maintenance of drug concentration over long periods of time – rapid absorption is unnecessary. In order to project a potential dose for use in prophylactic trials using our projected dose from the bradykinin challenge model (an acute treatment model), we relied on a similar acute-to-prophylactic extrapolation utilized for products in the plasma kallikrein mechanism. Ecallantide is a polypeptide inhibitor of plasma kallikrein used for treatment of attacks. Similarly to icatibant, the short half-life of ecallantide makes it generally unsuitable for use in prophylaxis.

Lanadelumab-flyo is a monoclonal antibody with the same target as ecallantide but with higher potency and longer half-life. Lanadelumab-flyo is used for prevention of attacks. Clinical trials and published literature correlate the steady-state concentrations of lanadelumab-flyo (relative to its EC50) to the observed prophylactic control of attacks. Based on the observed potency of PHA121 in the bradykinin challenge, we believe we can utilize a similar concentration-above-EC50 approach to predict the required exposure of PHA121 to control attacks prophylactically.

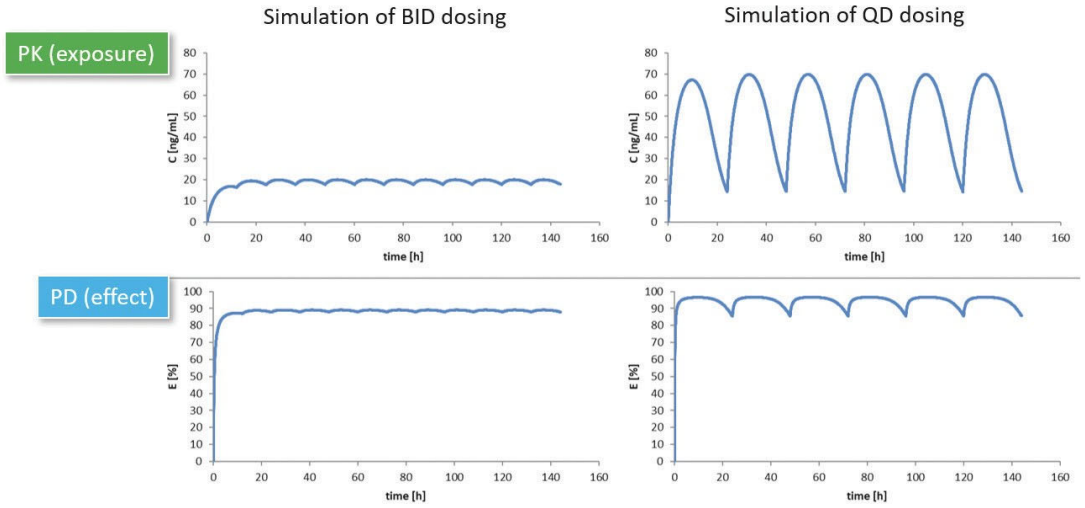
We believe we can achieve the concentrations desired for prophylactic activity with twice-daily dosing of the PHVS416 soft capsules. Therefore, in addition to the RAPIDe-1 on-demand trial, we are also planning clinical trials of PHVS416 to evaluate its efficacy and safety for preventing HAE attacks (prophylaxis). These include an evaluation of patients randomized to placebo or active doses for a treatment period with the primary objective to assess the safety profile of PHVS416 dose regimens for prophylactic treatments in HAE patients.

We also intend to conduct a registration-directed randomized, placebo-controlled evaluation in HAE prophylaxis to provide the key efficacy and safety evaluation of prophylactic treatment. We anticipate that PHVS719, as described below, will be included in this pivotal trial, with doses selected based on the PK performance of PHVS719 in Phase 1 trials. We also expect that the data from RAPIDe-1 will support the final dose selection for the prophylactic trials. Additional trials may be required by the FDA, EMA or other regulators even if we receive positive data from RAPIDe-1.

In order to provide a differentiated product featuring more consistent exposure of PHA121 for the prophylactic setting, we are developing an extended-release, or XR, formulation (PHVS719) that will feature continuous slow release maintaining PHA121 concentrations above the levels we predict to provide protection against attacks. PHA121 has demonstrated properties favorable to the development of XR formulations, and we believe that we will begin human pharmacokinetics trials with PHVS719 in 2021 to enable use of this product candidate in the pivotal prophylactic trial.

We believe that we have already identified a promising prototype formulation for extended release. The nonlinear mixed-mode model from our BK challenge trial allows us to simulate different formulations by changing certain formulation-related inputs, such as the in-vitro release rate, while utilizing the experimentally determined properties of PHA121, such as half-life, potency, and effect on BK-induced hemodynamic parameters (surrogate assessment). As shown in the graphs below, utilizing this mathematical model, we simulated the human PK/PD parameters of a prototype extended-release formulation, based on initial in vitro dissolution experiments. These modeling calculations suggest that

this prototype may already support twice-a- day dosing in patients, and we are continuing to refine our formulation with the goal of achieving once-a-day dosing. We are also planning to initiate a Phase 1 clinical trial with PHVS719 in 2021 before conducting the trial of PHVS719 in the prophylactic setting. We recently completed the 30-day review period with respect to our IND application for developing PHVS416 in the prophylactic indication, and we remain on track to initiate the clinical trial for prophylaxis treatment in 2021.



Simulation of pharmacokinetics (exposure) and pharmacodynamics (inhibition of bradykinin effect) for once-daily (QD) or twice-daily (BID) dosing of a prototype extended-release formulation, based on observed in vitro release characteristics

In addition, we also plan to run an open-label extension study in the prophylactic setting with both rollover and non-rollover subjects to collect longer duration safety data, which will be further discussed with FDA and EMA.

Intellectual Property

We seek to protect and enhance the proprietary technologies, inventions, product candidates, methods of manufacture and methods of usage of our product candidates, and improvements thereof that are commercially important to the development of our business. We protect our proprietary intellectual property by, among other things, filing patent applications in the United States and internationally covering our proprietary technologies, inventions, product candidates, methods of manufacture and use, and improvements that are important to the development and implementation of our business. We will also seek to rely on regulatory protection afforded by orphan drug designations, inclusion in expedited development and review, data exclusivity, market exclusivity and patent term extensions where available.

As of May 1, 2021, we own one U.S. patent that expires on November 23, 2038 and 32 pending patent applications worldwide, including one pending U.S. continuation application, 29 pending non-U.S. applications, including applications in Europe and Japan, and two pending PCT applications. The U.S. patent and 31 of these pending patent applications contain composition-of-matter claims to the PHA121 small molecule and derivatives thereof; PHA121 is the active pharmaceutical ingredient in, and therefore extends our patent applications to, our PHVS416 and PHVS719 product candidates. Each such patent application can generally be categorized into one of three patent families: (1) those relating to the novel bradykinin-B2-receptor antagonists, (2) those relating to the cyclic bradykinin-B2-receptor

antagonists, and (3) those relating to the new cyclic bradykinin-B2-receptor antagonists. One pending European patent application contains claims directed to the use of PHA121 in on- demand treatment of HAE and in prophylaxis for HAE, and accordingly extends the patent applications to methods of use of the PHVS416 and PHVS719 product candidates. Not accounting for any patent term adjustment, regulatory extension or terminal disclaimers, and assuming that all annuity and/or maintenance fees are paid timely, these patent applications, if granted, will not expire until November 24, 2038. We also rely upon trade secrets that may be important to the development of our business. Trade secrets are difficult to protect and provide us with only limited protection. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any patents that may be issued in the future.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries in which we have filed, including the U.S., the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the U.S., a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted for a portion of the term effectively lost as a result of the FDA regulatory review period, subject to certain limitations and provided statutory and regulatory requirements are met. Any such patent term extension can be for no more than five years, only one patent per approved product can be extended, the extension cannot extend the total patent term beyond 14 years from approval and only those claims covering the approved drug, a method for using it or a method for manufacturing, it may be extended. We may not receive an extension if we fail to exercise due diligence during the testing phase or regulatory review process, fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. In the future, if and when our product candidates receive approval from the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents we may obtain in the future covering PHA121, depending upon the length of the clinical trials for each product and other factors.

As with other biotechnology and pharmaceutical companies, our ability to establish and maintain our proprietary and intellectual property position for our product candidates will depend on our success in obtaining effective patent claims and enforcing those claims if granted. There can be no assurance that any of our current or future patent applications will result in the issuance of patents or that our future issued patents (if any) will provide meaningful protection of our product candidates or technology. For more information regarding the risks related to our intellectual property, see chapter 3.2 of this report.

License Agreement

On March 31, 2016, we entered into a license agreement (the "AnalytiCon License") and a research agreement with AnalytiCon to collaborate for the development of an orally available bradykinin B2 receptor antagonist. Pursuant to the AnalytiCon License, we acquired a worldwide, exclusive license from AnalytiCon to use (i) a certain proprietary substance class of bradykinin B2 receptor antagonist with the potential of oral activity ("OB2RA") and (ii) any derivatives, improvements, analogs, isomers, metabolites, or conjugates therefrom (together "OB2RA Class"), in each case, for the purpose of developing, manufacturing and marketing compounds on a global basis from the OB2RA Class for the

treatment of, among others, hereditary angioedema. Certain rights associated with PHA121, PHVS416 and PHVS719 are subject to the AnalytiCon license agreement. In consideration for the license, we paid AnalytiCon a non-refundable up-front payment of €250,000.

Under the AnalytiCon License, we are required to pay AnalytiCon one-time payments in an aggregate amount of up to €11.4 million upon the achievement of certain development, regulatory, and sales milestones. To date, we have paid AnalytiCon an aggregate amount of €1,150,000 (€250,000 up-front plus €900,000 in milestone payments), and €11 million in aggregate potential milestone payments remain outstanding. In addition, we will be required to pay AnalytiCon low to medium single-digit tiered royalties on direct or indirect net sales of licensed products. The royalties that we are required to pay AnalytiCon under this agreement may be reduced on a country-by-country and product-by-product basis if sales of a generic version of a product account for 1% or more of the relevant market.

Our agreement with AnalytiCon will expire upon the expiry of the last patent of the licensed intellectual property. Not accounting for any regulatory extension or terminal disclaimers, and assuming that all annuity and/ or maintenance fees are paid timely, the applicable expiration date is November 23, 2038. Either party may terminate the agreement prematurely for cause, in particular, for the other party's (i) uncured material breach, (ii) bankruptcy or insolvency, or (iii) challenge to the validity or ownership of the intellectual property rights relating to the compounds that form the object of the collaboration with AnalytiCon. If AnalytiCon were to (a) terminate the AnalytiCon License for cause and (b) exercise contractual remedies available to it thereunder, then we could be required to grant to AnalytiCon an exclusive worldwide license to our intellectual property generated under the collaboration with AnalytiCon for use in all applications, including HAE. In addition, we could be prevented from competing with AnalytiCon until five years after the commercial launch of any product containing a compound from the OB2RA Class.

Manufacturing and Supply

We currently have a single contract CDMO for the production of PHA121 API. A robust and scalable synthetic route has been established. All raw materials can be purchased from multiple suppliers. We plan to identify and qualify a second CDMO. We also collaborate with a leading CDMO for the manufacturing of the on-demand treatment product PHVS416. With the same CDMO we are currently optimizing the prophylactic treatment product PHVS719. The CDMO is also responsible for packaging and worldwide distribution of commercial drug products.

Sales and Marketing

The Pharvaris team, including its founders, have experience developing and commercializing drug products for rare diseases including HAE specifically. We intend to develop a fully integrated sales and marketing organization ahead of marketing approval for PHVS416 or PHVS719. Even though HAE is a competitive market, orphan product companies have demonstrated successful first launches with excellent preparation and execution. We believe that our products will provide patients with significant new treatment options, and we will evaluate options to optimize the commercial opportunity.

Competition

The biotechnology industry is characterized by rapidly advancing technologies, intense competition and a strong emphasis on intellectual property. We face competition from different sources, including from academic centers as well as from a number of large and specialty biotechnology and pharmaceutical companies.

Currently, there are several licensed therapies for HAE, including the following:

- *FIRAZYR*: The BK receptor antagonist FIRAZYR (icatibant) is approved by the FDA in the U.S. and by regulators globally for the treatment of acute attacks and is administered by subcutaneous administration. Six generic forms of icatibant have been approved in the U.S. since July 2019 and more may be approved in the future.
- *C1-INH*: C1-INH replacement therapy is available in the U.S. and globally as an acute therapy (BERINERT CINRYZE, and CETOR) and as a prophylactic therapy (HAEGARDA/BERINERT 2000/3000 and CINRYZE). These therapies are dosed subcutaneously and intravenously. Recombinant C1-INH (Ruconest) is also available in the U.S. and in Europe as an acute therapy.
- *Kallikrein Inhibitors*: KALBITOR (ecallantide) is a specific recombinant plasma kallikrein inhibitor that is dosed subcutaneously by healthcare providers in the U.S. to treat acute HAE attacks. TAKHZYRO (lanadelumab-flyo) is a monoclonal antibody approved in the U.S. and a growing number of countries for prophylaxis of HAE attacks and can be self-administered as a subcutaneous injection. ORLADEYO (berotralstat) is a kallikrein inhibitor that was approved in the U.S. in the fourth quarter of 2020 and is dosed orally once-daily for the prevention of HAE attacks.
- *Other Medications*: Prophylactic administration of synthetic attenuated androgens (generically available as danazol or stanozolol) has been *utilized* to reduce the frequency or severity of attacks. However, long-term use of danazol or stanozolol may result in liver damage, virilization and arterial hypertension. Six-month liver function tests, annual lipid profiles, and biennial hepatic ultrasound are recommended for patients on chronic androgen therapy.

We are also aware of a number of HAE therapies in clinical development. Currently, there are three orally delivered plasma kallikrein inhibitors being developed clinically: Kalvista's KVD900 for acute treatment and KVD824 for prophylactic treatment and Attune's ATN-249 for prophylactic treatment. Additionally, CSL is developing garadacimab, an anti-factor XIIa mAb for prophylactic treatment, which is delivered subcutaneously or intravenously, and Ionis's IONIS-PKK-LRx, an antisense oligonucleotide inhibitor of prekallikrein for prophylactic treatment, which is delivered subcutaneously.

Many of our competitors and potential competitors have substantially greater scientific, research and product development capabilities as well as greater financial, manufacturing, commercialization and human resources than we do. In addition, there is intense competition on the clinical trial sites and the enrollment of HAE patients for clinical trials. Many specialized biotechnology firms have formed collaborations with large, established companies to support the research, development and commercialization of products that may be competitive with ours, and many other biotech and pharmaceutical companies are competing for the same potential employees. Accordingly, our competitors may be more successful than we may be in developing, manufacturing, commercializing

their products and in achieving widespread market acceptance.

Government regulation and product approval

In each country where we conduct our research and development, manufacture our products and intend to market our product candidates, if approved, we must comply with laws and regulations, including regulations issued by regulatory agencies and by other national or supra-national regulatory authorities, or collectively, the Competent Authorities, as well as industry standards, that govern nearly all aspects of our activities. Among others, the FDA, the EMA and the national Competent Authorities of each Member State of the European Union are the key regulatory agencies that exercise oversight over all aspects of our products.

Our pharmaceutical product candidates are subject to substantial requirements that govern, among other things, their research, development, testing, manufacturing, quality control, approval, safety, efficacy, labelling, storage, record keeping, commercialization, distribution, import and export, post-approval monitoring and reporting, advertising, promotion, reimbursement and pricing. The process of maintaining continued compliance with the regulatory requirements requires the expenditure of substantial amounts of time and money.

The nonclinical and clinical development paths for product candidates are broadly similar in the European Union and the United States.

Nonclinical Studies

Development of the product candidates starts with nonclinical studies, which include laboratory tests to develop a robust product manufacturing process, including formulation and stability. In addition, nonclinical studies are conducted to evaluate the mode of action and in vivo tests are conducted until adequate proof of safety is established (e.g., animal testing for reproductive toxicity and carcinogenicity). The conduct of the nonclinical tests and formulation of the compounds for testing must comply with regulations and requirements set by the Competent Authorities, including compliance with GLP. Upon successful completion of nonclinical studies, clinical development can be initiated.

Clinical Studies

Prior to obtaining approval to commercialize a drug candidate, sponsors typically must demonstrate with substantial evidence from well-controlled clinical trials, and to the satisfaction of the Competent Authorities, that such drug candidates are safe and effective for their intended uses. Clinical trials involve the administration of the investigational product to healthy volunteers or subjects under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with the requirements of the Competent Authorities; (ii) in compliance with GCP, an international standard meant to protect the rights and health of subjects and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. The number of clinical studies and trials that will be required for approval varies depending on, e.g., the drug candidate and the disease or condition that the drug candidate is designed to address.

Prior to initiating clinical trials, a request for clinical trial authorization (national Competent Authorities in the European Union) or an IND, application in the United States must be submitted to the

relevant Competent Authorities. These submissions must be supported by an investigational medicinal product dossier or equivalent as detailed in applicable regulations and guidance documents from the Competent Authorities. Extensive information about the proposed clinical studies, as well as the results of the nonclinical tests, together with manufacturing information and analytical data, are included in these submissions. In the United States, a 30-day waiting period after the submission of an IND is required prior to the commencement of clinical testing in humans. If the FDA, has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin.

Manufacturing of investigational products is subject to authorization and must be carried out in accordance with cGMP. Furthermore, a clinical trial may only be started after an IRB (United States) or a competent Ethics Committee (European Union) has issued a favorable opinion on the clinical trial application.

During all phases of clinical development, Competent Authorities require extensive monitoring and auditing of all clinical activities, clinical data and clinical trial investigators. Annual progress reports detailing the progress of the clinical trials must be submitted to the Competent Authorities. Important new safety information, that suggests a significant risk for human patients, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure, must also be provided to clinical investigators.

The Competent Authorities, sponsor or its data safety monitoring board may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research exposes patients to an unacceptable health risk. Similarly, an IRB or Ethics Committee can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the institutional requirements or if the drug candidate has been associated with unexpected serious harm to patients.

The following section describes specific regulatory regimes and regulations applicable in certain jurisdictions.

United States

U.S. Food and Drug Administration

In the United States, FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FFDCA, and implementing regulations. These laws, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-marketing monitoring and reporting, sampling, and import and export of drug products. The process of obtaining regulatory approvals and the subsequent compliance with the many statutory and regulatory provisions require the expenditure of substantial time and financial resources. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as clinical hold, FDA refusal to approve pending regulatory applications, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties, and criminal prosecution.

The FDA Approval Process

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase 1, the initial introduction of the product

candidate is usually into healthy human subjects, and the product candidate is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Phase 2 usually involves trials in a limited patient population to determine the effectiveness of the product candidate for a particular indication, dosage tolerance, and optimal dosage, and to identify common adverse effects and safety risks. If a product candidate demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to obtain additional information about clinical efficacy and safety in a larger number of subjects, typically at geographically dispersed clinical trial sites, to permit the FDA to evaluate the overall benefit-risk relationship of the product candidate and to provide adequate information for the labeling of the product candidate. In most cases, the FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the product candidate. A single Phase 3 trial may be sufficient in certain circumstances.

During the development of a new product candidate, sponsors are given opportunities to meet with the FDA at certain points; specifically, prior to the submission of an IND, at the end of Phase 2 and before an NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date and for the FDA to provide advice on the next phase of development. Sponsors typically use the meeting at the end of Phase 2 to discuss their Phase 2 clinical results and present their plans for the pivotal Phase 3 clinical trials that they believe will support the approval of the new product candidate.

The results of drug candidate development, nonclinical testing, clinical trials and proposed labeling are submitted to the FDA as part of the New Drug Application, or NDA. An NDA must include all information regarding and data from pertinent nonclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the drug's chemistry, manufacturing and controls. The FDA will accept, as support for an IND or NDA a well-designed, well-conducted, non-IND foreign clinical trial if it was conducted in accordance with GCP and the FDA is able to validate the data from the trial through an on-site inspection, if necessary. Regulatory applications based solely on foreign clinical data meeting these criteria may be approved if the foreign data are applicable to the U.S. population and U.S. medical practice, the trials have been performed by clinical investigators of recognized competence, and the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria may result in the application not being approvable based on the foreign data alone. To support marketing approval and authorization, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug to the FDA's satisfaction.

The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee payment to FDA, and the manufacturer and/or sponsor under an approved NDA are also subject to certain annual program user fees. The FDA typically increases these fees annually.

The FDA has 60 days from its receipt of an NDA to determine whether it will accept the application for filing based on the agency's threshold determination that the application is sufficiently complete to permit substantive review. The FDA may refuse to file any NDA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the NDA must be resubmitted with the additional information and the resubmitted application also is subject to review before the FDA accepts it for filing. Once the FDA accepts the filing, the FDA

begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Under the Prescription Drug User Fee Act, the FDA has a goal of responding to standard review NDAs within ten months after the 60-day filing review period, but this timeframe is often extended. The FDA reviews most applications for standard review drugs within twelve months. The review process may be extended by the FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission. This late- submitted information is typically requested by FDA.

The FDA may also refer applications for novel drugs or product candidates that present difficult questions of safety or efficacy, to an FDA Advisory Committee. An Advisory Committee is an outside panel that typically includes clinicians and other experts in the field that will review and evaluate the questions posed by FDA, and provide recommendations, sometimes including whether the FDA should approve the application. The FDA is not bound by the recommendation of an Advisory Committee, but it generally follows such recommendations.

Before approving an NDA, the FDA will typically inspect one or more clinical study sites to assure compliance with GCP. The FDA may also inspect one or more nonclinical study sites. In addition, the FDA will inspect the facility or the facilities involved in the manufacture of the drug to determine if the facilities, processes and quality are compliant with cGMP. The FDA will not approve an NDA unless compliance with cGMP is satisfactory.

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter indicates that the FDA has completed its review of the NDA, and the agency has determined that it will not approve the application in its present form. A complete response letter generally outlines the deficiencies in the NDA, which may be minor or substantial, and may delineate the requirements needed to successfully progress the NDA to approval. This may require substantial additional clinical data and/or other significant, expensive, and time-consuming requirements related to clinical studies, preclinical studies and/or manufacturing. If a complete response letter is issued, the applicant may either resubmit the NDA, addressing the deficiencies identified in the letter, or withdraw the application. The FDA has committed to reviewing resubmissions of the NDA addressing such deficiencies in two or six months, depending on the type of information included. Even if such data is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval.

An approval letter authorizes commercial marketing of the drug, with specific prescribing information for specific indications. Even if FDA approves the NDA, the approval may be significantly limited to specific indications and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a risk evaluation and mitigation strategy, or REMS, or otherwise limit the scope of any approval. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the product. In addition, the FDA may require confirmatory post-marketing trials, sometimes referred to as "Phase 4" clinical trials, designed to further assess a product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Expedited Approval in the U.S.

The FDA has a number of programs that are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition. These are: Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval and Priority Review Designation.

Fast Track Designation can be requested early in the development process, if evidence of activity in a nonclinical model, a mechanistic rationale or pharmacologic data demonstrates the potential to address an unmet medical need. In the later stages of development, available clinical data should demonstrate the potential to address an unmet medical need. Fast Track Designation provides opportunities for applicants to have frequent interactions with the relevant FDA review teams. In addition, a Fast Track product can be eligible for priority review if supported by clinical data at the time of NDA submission. If the FDA determines that a Fast Track product may be effective after preliminary evaluation of the NDA, it may consider reviewing portions of a marketing application before the sponsor submits the complete application. Fast Track Designation can be requested when the IND is first submitted or at any time thereafter but before receiving approval of the NDA. As a practical matter, the FDA should ordinarily receive a Fast Track Designation request no later than the sponsor's pre-NDA meeting with the agency because many of the features of Fast Track Designation will not apply after that time. The FDA will respond to Fast Track Designation requests within 60 calendar days of receipt of the request.

The FDA's Breakthrough Therapy Designation is intended to expedite the development and review of drugs which may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. A drug that receives Breakthrough Therapy Designation is eligible for all Fast Track Designation features, intensive guidance from FDA on an efficient drug development program, beginning as early as Phase 1, and organizational commitment involving senior managers. Breakthrough Therapy Designation is requested by the manufacturer. A sponsor needs to submit a request to the agency for Breakthrough Therapy Designation, but in some cases the FDA may suggest that the sponsor consider submitting a request after reviewing submitted data and information (including preliminary clinical evidence), the FDA thinks the drug development program may meet the criteria for Breakthrough Therapy Designation; and the remaining drug development program can benefit from the designation. Ideally, a Breakthrough Therapy Designation request should be received by the FDA no later than the End-of-Phase 2 meetings if any of the features of the designation are to be obtained. The FDA will respond to Breakthrough Therapy Designation requests within 60 days of receipt of the request.

Accelerated approval may be granted for a product based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. For drugs granted accelerated approval, post-marketing confirmatory trials will be required to verify and describe the anticipated effect on the IMM or other clinical benefit. The accelerated approval pathway has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug. Accelerated approval is also potentially

useful in acute disease settings where the intended clinical benefit can be demonstrated only in a very large study because the clinical event that would need to be evaluated to demonstrate clinical benefit occurs rarely.

The FDA may withdraw approval of a drug or indication approved under the accelerated approval pathway if e.g., the confirmatory trial fails to verify the predicted clinical benefit, the evidence demonstrates that the product is not shown to be safe and effective under the conditions of use, the applicant fails to conduct the post- approval trials with due diligence or the applicant disseminates false or misleading promotional materials related to the product.

A priority review designation is intended to direct overall attention and resources to the evaluation of an application for a drug that treats, prevents or is used in the diagnosis of a serious condition and if approved would provide a significant improvement in safety or effectiveness. Eligibility for priority review is determined by the FDA at the time of an NDA or efficacy supplement filing. Where an application receives a priority review designation, the FDA's goal is to take action on the marketing application within six months of receipt (as compared to within 10 months under standard review). The FDA determines whether an application qualifies for priority review (versus standard review) for every application it reviews, not just when priority review is requested by the applicant. However, an applicant may expressly request priority review. The FDA will inform the applicant in writing of a priority review designation by day 60 of the review.

Orphan Designation

An orphan drug designation qualifies the manufacturer for certain tax credits and may lead to market exclusivity for seven years following the date of the drug's approval by the FDA. The FDCA provides that a drug shall be designated as an orphan drug if its manufacturer can establish that the drug is for a condition that affects fewer than 200,000 individuals in the United States or when there is no reasonable expectation that the cost of developing and making available the drug for the disease or condition will be recovered from sales of the drug in the United States. More than one manufacturer may receive orphan drug designation for the same drug for the same rare disease or condition, but each manufacturer seeking orphan drug designation must file a complete request for designation.

In the United States, a manufacturer may request orphan drug designation of a previously unapproved drug or new orphan indication for a different use for an already marketed drug. In addition, a manufacturer of a drug that is otherwise the same drug as an already approved orphan drug may seek and obtain orphan drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug. FDA may grant the drug orphan exclusivity upon approval if clinical superiority is demonstrated. Orphan drug exclusivity cannot otherwise be granted for the same drug made by another manufacturer for the same indication during the market exclusivity period unless the original manufacturer consents or the original manufacturer is unable to ensure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated.

An application for orphan drug designation can be made any time prior to the filing of an application for approval to market the product. The period of orphan exclusivity, if granted, begins on the date that the marketing application is approved. The exclusivity is limited to the indication for which the drug has been approved.

Post-Marketing Requirements

FDA may withdraw approval of an NDA if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product may result in restrictions on the product, product recalls or even complete withdrawal of the product from the market.

After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval; such changes may require the approval of a new NDA or an NDA supplement. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing new NDAs. As with new NDAs, the FDA often significantly extends the review process with requests for additional information or clarification. In addition, the FDA may, under some circumstances, require testing and surveillance programs to monitor the effect of approved products that have been commercialized, and the FDA under some circumstances has the power to prevent or limit further commercialization of a product based on the results of these post-marketing programs.

In addition, drug products manufactured or distributed pursuant to FDA approvals, are subject to additional and continuing regulation by the FDA, including, among other things:

- record-keeping requirements;
- reporting of adverse experiences associated with the product;
- providing the FDA with updated safety and efficacy information;
- distribution of drug samples;
- notifying the FDA and gaining its approval of specified manufacturing or labeling changes;
- drug establishment registration and drug listing requirements; and
- complying with FDA promotion and advertising requirements, which include, among other things, standards for direct-to-consumer advertising, restrictions on promoting products for uses or in patient populations that are not described in the product's approved labeling, limitations on industry-sponsored scientific and educational activities and requirements for promotional activities involving the internet.

Drug manufacturers are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP requirements and other laws. There are strict regulations regarding changes to the manufacturing process, and, depending on the significance of the change, it may require prior FDA approval before it can be implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon drug manufacturers. Drug manufacturers must also satisfy the product tracing, verification and reporting requirements in the Drug Quality and Security Act and have procedures in place to identify and properly handle suspect and illegitimate product. Accordingly, manufacturers must continue to expend time, money and effort in the area of production, distribution and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

Sponsors of clinical trials of FDA-regulated products are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, trial sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to disclose the results of their clinical trials after completion.

Disclosure of the results of these trials can be delayed in certain circumstances for up to two years after the date of completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Although rare, the FDA may withdraw approval of an NDA if a company does not comply with its extensive regulatory requirements or if significant safety, efficacy or manufacturing issues arise after the drug reaches the market. More typically, if a company or the FDA discovers previously unknown problems with a drug, including adverse events of unanticipated severity or frequency or issues with manufacturing processes, the FDA may revise the approved labeling to add new safety information; require additional clinical studies to assess new safety risks; or impose distribution or other restrictions under a REMS program. Other potential consequences may include:

- restrictions on the commercialization or manufacturing of the drug, market withdrawals or recalls;
- fines, warning letters or holds on post-approval clinical studies;
- the FDA refusal to approve pending NDAs or supplements to approved NDAs;
- drug seizure or detention, or refusal to permit the import or export of drugs; or
- injunctions or the imposition of civil or criminal penalties.

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the testing, approval, manufacturing and marketing of products regulated by the FDA. In addition to new legislation, FDA regulations and policies are often revised or interpreted by the agency in ways that may significantly affect our business and product candidates. It is impossible to predict whether further legislative changes will be enacted or whether FDA regulations, guidance, policies or interpretations will be changed or what the effect of such changes, if any, may be.

U.S. Patent Term Restoration

A patent claiming a new product may be eligible for a limited patent term extension under the Hatch- Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of a clinical investigation involving human beings is begun and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. In addition, the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Other U.S. Healthcare Laws and Compliance Requirements

In the United States, our activities are potentially subject to regulation by various federal, state

and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, sales, marketing and scientific/educational grant programs are subject to anti-fraud and abuse provisions of the Social Security Act, the false claims laws, the privacy provisions of HIPAA (defined below), transparency reporting laws, and similar state laws, each as amended. Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to these broadly applicable healthcare laws and regulations that may constrain our business and/or financial arrangements.

The applicable federal and state healthcare laws and regulations, include, without limitation, the following:

- *The Federal Anti-Kickback Statute* – An intent-based federal criminal statute that prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order, recommendation, or arranging of, any item or service for which payment may be made, in whole or in part, by a federal health care program such as Medicare or Medicaid. The term "remuneration" has been interpreted broadly to include anything of value. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively, "PPACA"), among other things, amended the intent requirement of the federal Anti-Kickback Statute to clarify that a person or entity need not have actual knowledge of this statute or specific intent to violate it. The Anti-Kickback Statute applies to arrangements between pharmaceutical manufacturers on the one hand and individuals, such as prescribers, patients, purchasers, and formulary managers on the other hand, including, for example, consulting/speaking arrangements, discount and rebate offers, grants, charitable contributions, and patient support offerings, among others. A conviction for violation of the Anti-Kickback Statute can result in criminal fines and/or imprisonment and requires mandatory exclusion from participation in federal health care programs. Exclusion may also be imposed if the government determines that an entity has committed acts that are prohibited by the Anti-Kickback Statute. Although there are a number of statutory exceptions and regulatory safe harbors to the federal Anti-Kickback Statute that protect certain common industry activities from prosecution, the exceptions and safe harbors are drawn narrowly and arrangements may be subject to scrutiny or penalty if they do not fully satisfy all elements of an available exception of safe harbor. The Anti-Kickback Statute safe harbors are the subject of possible regulatory reforms. Any changes to the safe harbors may impact our future contractual and other arrangements with pharmacy benefit managers, group purchasing organizations, third-party payors, wholesalers and distributors, healthcare providers and prescribers, and other entities, as well as our future pricing strategies.
- *The Federal Civil False Claims Act*—Imposes civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment to a federal health care program or knowingly making using or causing to be made or used a false

statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $11,665 to $22,331 per false claim or statement for penalties assessed after June 19, 2020, with respect to violations occurring after November 2, 2015. Pharmaceutical companies have been investigated and/or subject to government enforcement actions asserting liability under the federal civil False Claims Act in connection with their alleged off-label promotion of drugs, purportedly concealing price concessions in the pricing information submitted to the government for government price reporting purposes (e.g., under the Medicaid Drug Rebate Program), and allegedly providing free product to customers with the expectation that the customers would bill federal health care programs for the product. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes "any request or demand" for money or property presented to the U.S. government. In addition, manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. There is also the Federal Criminal False Claims Act, which is similar to the Federal Civil False Claims Act and imposes criminal liability on those that make or present a false, fictitious or fraudulent claim to the federal government.

- *The Federal Criminal Statute on False Statements Relating to Health Care Matters*—Makes it a crime to knowingly and willfully falsify, conceal, or cover up a material fact, make any materially false, fictitious, or fraudulent statements or representations, or make or use any materially false writing or document knowing the same to contain any materially false, fictitious, or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items, or services.
- *Criminal Health Care Fraud Statute*—Enacted as part of the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), makes it a crime to knowingly and will fully execute, or attempt to execute, a scheme or artifice to defraud any health care benefit program or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program in connection with the delivery of or payment for healthcare benefits, items or services.
- *The Federal Civil Monetary Penalties Law*—Authorizes the imposition of substantial civil monetary penalties against an entity, such as a pharmaceutical manufacturer, that engages in activities including, among others (1) knowingly presenting, or causing to be presented, a claim for services not provided as claimed or that is otherwise false or fraudulent in any way; (2) arranging for or contracting with an individual or entity that is excluded from participation in federal health care programs to provide items or services reimbursable by a federal health care program; (3) violations of the federal Anti-Kickback Statute; or (4) failing to report and return a known overpayment.
- *HIPAA Health Information Privacy and Security*—HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("HITECH"), imposes privacy, security, and breach reporting obligations on certain covered entity healthcare providers, health plans, and healthcare clearinghouse as well as their business associates that perform certain services involving the use or disclosure of individually identifiable health

information, including, among other requirements, mandatory contractual terms and technical safeguards to protect the privacy, security and transmission of individually identifiable health information, and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in U.S. federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

- *The Federal Physician Payments Sunshine Act*—Requires "applicable manufacturers" of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program, among others, to track and report annually to the federal government (for disclosure to the public) certain payments and other transfers of value they make to "covered recipients." The term covered recipients includes U.S.-licensed physicians, teaching hospitals, and, for reports submitted on or after January 1, 2022, physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse midwives. Failure to submit required information may result in civil monetary penalties.
- *Analogous State Laws*—There are state law equivalents of the above federal laws, such as the Anti- Kickback Statute and the False Claims Act, which may apply to items and services reimbursed by any third-party payor, including commercial insurers (i.e., so-called "all-payor anti-kickback laws").
- *State Laws Regulating Pharmaceutical Manufacturer Compliance Programs, Drug Price Transparency, and Other Practices*—Some state laws require pharmaceutical companies to implement compliance programs, comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or to track and report gifts, compensation, or other remuneration to physicians and other healthcare providers. Several U.S. states and localities have enacted legislation requiring pharmaceutical companies to establish marketing compliance programs, file periodic reports, and/or make periodic public disclosures on sales, marketing, pricing, clinical trials, and other activities. Other state laws prohibit certain marketing-related activities including the provision of gifts, meals or other items to certain healthcare providers, and restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs. In addition, several recently passed state laws require disclosures related to state agencies and/or commercial purchasers with respect to certain price increases that exceed a certain level as identified in the relevant statutes. Some of these laws and regulations contain ambiguous requirements that government officials have not yet clarified. Given the lack of clarity in the laws and their implementation, our reporting actions could be subject to the penalty provisions of the pertinent federal and state laws and regulations.
- We are also required to satisfy the product tracing, verification and reporting requirements set out in the Drug Quality and Security Act.

We expect that one or more of our products, if approved, may be eligible for coverage under

Medicare, the federal health care program that provides health care benefits to the aged and disabled, including coverage for outpatient services and supplies, such as certain drug products, that are medically necessary to treat a beneficiary's health condition. In addition, one or more of our products, if approved, may be covered and reimbursed under other federal health care programs, such as Medicaid and the 340B Drug Pricing Program. The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services and pay quarterly rebates based on utilization of the manufacturer's drugs under the program as a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. Under the 340B Drug Pricing Program, the manufacturer must extend discounts to entities that participate in the program. As part of the requirements to participate in these government programs, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average manufacturer price and best price.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations, guidance, case law or other applicable law. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, individual imprisonment, exclusion from participation in federal health care programs, such as Medicare and Medicaid, disgorgement, reputational harm, additional oversight and reporting obligations pursuant to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with applicable laws and regulations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to market our products, if approved, and adversely impact our financial results. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws and regulations, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management's attention from the operation of our business, even if our defense is successful. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, it may be costly to us in terms of money, time and resources, and they may be subject to criminal, civil or administrative sanctions, including exclusions from government-funded healthcare programs.

U.S. Healthcare Reform

In the United States, there have been and continue to be a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of our future collaborators, to effectively sell any drugs for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and additional downward pressure on the price that we, or our future collaborators, may receive for any approved drugs. For example, the PPACA substantially changed and continues to impact healthcare financing and delivery by both government payors and private insurers. Among the PPACA provisions of importance to the pharmaceutical industry, in addition to those otherwise described above, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, which include, among other things, new government investigative powers and enhanced penalties for non-compliance;
- establishment of the Medicare Part D coverage gap discount program that, as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D, requires manufacturers to provide a now 70% point-of-sale discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of the types of entities eligible for discounts under the Public Health Service pharmaceutical pricing program (i.e., the 340B program);
- reporting of certain financial arrangements between manufacturers of drugs, biologics, devices, and medical supplies and physicians and teaching hospitals under the Physician Payments Sunshine Act;
- a requirement to annually report certain information regarding drug samples that manufacturers and distributors provide to licensed practitioners; and
- creation of the Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Since its enactment there have been judicial and Congressional challenges to certain aspects of the PPACA.

While Congress has not enacted legislation to comprehensively repeal the PPACA, at least two bills affecting the implementation of the PPACA have been signed into law, including the repeal, effective January 1, 2019, of the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly referred to as the "individual mandate." In December 2018, a federal district court in Texas ruled that the PPACA's individual mandate, without the penalty that was repealed effective January 1, 2019, was unconstitutional and could not be severed from the PPACA. As a result, the court ruled the remaining provisions of the PPACA were also invalid. The Fifth Circuit Court of Appeals affirmed the district court's ruling that the individual mandate was unconstitutional, but it remanded the case back to the district court for further analysis of whether the mandate could be severed from the PPACA (i.e., whether the entire PPACA was therefore also unconstitutional). The Supreme Court of the United States granted certiorari on March 2, 2020, heard oral arguments on November 10, 2020 and the case is expected to be decided in 2021.

The President of the United States has also previously signed several Executive Orders, directives, and legislation affecting certain provisions of the PPACA. For example, effective January 1, 2019, the Bipartisan Budget Act of 2018, or the BBA, among other things, further amended portions of

the Social Security Act implemented as part of the PPACA to increase from 50% to 70% the point-of-sale discount that pharmaceutical manufacturers who participate in the Medicare Part D Coverage Gap Discount Program must provide to eligible Medicare Part D beneficiaries during the coverage gap phase of the Part D benefit, commonly referred to as the "donut hole," and to reduce standard beneficiary cost sharing in the coverage gap from 30% to 25% in most Medicare Part D plans. In the future, there may be additional challenges and/or amendments to the PPACA. Additionally, on December 20, 2019, President Trump signed appropriations legislation for fiscal year 2020 that repealed the PPACA's so-called "Cadillac" tax on certain high-cost employer-sponsored health insurance plans, for tax years beginning after December 31, 2019; the annual fee imposed on certain health insurance providers, for calendar years beginning after December 31, 2020; and the medical device excise tax on non-exempt medical devices, for sales after December 31, 2019. In the future, there may be additional challenges and/or amendments to the PPACA. It remains to be seen precisely what any new legislation will provide, when or if it will be enacted, and what impact it will have on the availability and cost of healthcare items and services, including drug products.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year effective April 1, 2013 and, due to subsequent legislation, will stay in effect through 2030 unless additional Congressional action is taken, with the exception of a temporary suspension of the payment reduction from May 1, 2020 through December 31, 2020 enacted as part of the CARES Act. Further, the American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments from providers from three to five years. These legislative changes may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Further, there has been heightened governmental scrutiny recently over the manner in which drug manufacturers set prices for their marketed products in the United States. Congress is considering various legislative proposals to further increase transparency around prices and price increases, lower out-of-pocket costs for consumers, and decrease spending on prescription drugs by government programs. On September 13, 2020, President Trump issued an executive order directing the Secretary of Health and Human Services to pursue implementation of two new payment models under which Medicare would test whether paying no more than the "most-favored-nation" price for certain included drugs and biological products covered under Part B and Part D, respectively, would mitigate poor clinical outcomes and increased Medicare expenditures associated with high drug costs. If implemented, the "most-favored-nation" price would generally reflect the lowest price, after certain adjustments, for a pharmaceutical product sold in an economically-comparable member country of the Organisation for Economic Co-operation and Development. Congress has also continued to conduct inquiries into the prescription drug industry's pricing practices. While several proposed reform measures will require Congress to pass legislation to become effective, Congress and the new Biden Administration have each indicated that it will continue to seek new legislative and/or regulatory measures to address prescription drug costs. At the state level, legislatures are increasingly passing legislation and states are implementing regulations designed to control spending on, and patient out-of-pocket costs for, drug products. Implementation of cost containment measures or other healthcare reforms that affect the pricing and/or availability of drug products may impact our ability to generate revenue, attain or maintain profitability,

or commercialize products for which we may receive regulatory approval in the future.

We expect that these, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved drug. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our drugs.

Privacy and Information Security

We may be subject to privacy and data security regulations and legal requirements in the United States and Europe. As we become more dependent on information technologies to conduct our operations, cyber incidents, including deliberate attacks and attempts to gain unauthorized access to computer systems and networks, may increase in frequency and sophistication. Our systems, servers and platforms and those of our service providers may be vulnerable to privacy and information security incidents such as data breaches, viruses or other malicious code, coordinated attacks, data loss, phishing attacks, ransomware, denial of service attacks, or other security or IT incidents caused by threat actors, technological vulnerabilities or human error. If we, or any of our vendors that support our IT or have access to our data, including any third party vendors that collect, process and store personal data on our behalf, fail to comply with laws requiring the protection of personal information, or fail to safeguard and defend personal information or other critical data assets or IT systems, we may be subject to regulatory enforcement and fines as well as private civil actions. We may be required to expend significant resources in the response, containment, mitigation of cybersecurity incidents as well as in defense against claims that our information security was unreasonable or otherwise violated applicable laws or contractual obligations.

In the United States, numerous federal and state laws and regulations, including federal health information privacy laws, state data breach notification laws, state health information privacy laws and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act), that govern the collection, use, disclosure and protection of health-related and other personal information could apply to our operations or the operations of our collaborators.

Domestic laws in this area are complex and developing rapidly. Many state legislatures have adopted legislation relating to privacy, data security and data breaches. Laws in all 50 states require businesses to provide notice to customers whose personally identifiable information has been disclosed as a result of a data breach. The laws are not consistent, and compliance in the event of a widespread data breach is costly. States are also frequently amending existing laws, requiring attention to frequently changing regulatory requirements.

Additionally, the Federal Trade Commission, or FTC, and state attorneys general enforce consumer protection laws that prohibit unfair and deceptive acts and practices, including Section 5 of the FTC Act, which creates standards for the collection, use, dissemination and security of health-related and other personal information. Claims of unfair or deceptive trade practices regarding privacy and security can lead to significant liabilities and consequences, including regulatory investigations, penalties, fines and orders as well as civil claims, which could impact our data practices and operations or cause reputational damage.

Further, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes requirements relating to the privacy,

security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards directly applicable to business associates, independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

We also may be subject to privacy and data security requirements in Europe. Any clinical trial programs we conduct or research collaborations we enter into in the European Economic Area, or EEA, may subject us to European data protection laws, including the EU General Data Protection Regulation 2016/679, or GDPR. We are subject to the GDPR (as implemented by countries in the EEA), which applies extra-territorially and imposes onerous requirements on controllers (e.g., sponsors) and processors (e.g., CROs, laboratories) of personal data, including, for example: (i) accountability and transparency requirements, and enhanced requirements for obtaining valid consent; (ii) obligations to consider data protection as any new products or services are developed and to limit the amount of personal data processed; (iii) obligations to comply with data protection rights of data subjects; and (iv) reporting of personal data breaches to the supervisory authority without undue delay (and no later than 72 hours). The GDPR also prohibits the international transfer of personal data from the EEA to countries outside of the EEA unless made to a country deemed to have adequate data privacy laws by the European Commission or where a data transfer mechanism has been put in place. Until recently, one such data transfer mechanism was the EU-US Privacy Shield. However, in July 2020 the Court of Justice of the European Union, or CJEU declared the Privacy Shield to be invalid. The CJEU upheld the validity of the standard contractual clauses, or SCCs, as a legal mechanism to transfer personal data but companies relying on SCCs will—subject to additional guidance from regulators in the EEA—need to evaluate and implement supplementary measures that provide privacy protections additional to those provided under SCCs. Further, the GDPR provides that countries in the EEA may establish their own laws and regulations further restricting the processing of certain personal data, including genetic data, biometric data, and health data.

Failure to comply with the GDPR requirements could result in regulatory investigations, enforcement notices requiring us to stop or change the way we use personal data and/or fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims for financial or non-financial loss by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill.

If our operations are found to be in violation of any of the data protection laws described above or any other laws that apply to us, we may be subject to penalties, including, but not limited to, criminal, civil and administrative penalties, damages, fines, disgorgement, individual imprisonment, possible exclusion from participation in government healthcare programs, injunctions, private qui tam actions brought by individual whistleblowers in the name of the government, class action litigation and the curtailment or restructuring of our operations, as well as additional reporting obligations and oversight if we become subject to a corrective action plan or other agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our results of operations.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or 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. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Additional Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

European Union

European Medicines Agency

Marketing approvals under the European Union regulatory system may be obtained through a centralized or the national marketing authorization procedures. The EMA and the European Commission administer the centralized authorization procedure. Pursuant to Regulation (EC) No. 726/2004 and Regulation (EC) 1394/2007, as amended, this procedure is compulsory for human medicines containing a new active substance to treat for which the therapeutic indication is the treatment of any of the following diseases: acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes, auto-immune diseases and other immune dysfunctions, viral diseases and all drugs that are designated as orphan drugs pursuant to Regulation (EC) No. 141/2000, as amended. Drugs for other indications may be granted a centralized authorization in accordance with Regulation (EC) No. 726/2004 if the drug contains a new active substance and is of a significant therapeutic, scientific or technical innovation or where the granting of authorization in accordance with Regulation (EC) No. 726/2004 is in the interests of patients or animal health at EU level.

When a centralized authorization is granted, the authorization is automatically valid in all Member States of the European Union and by extension in the European Economic Area, or EEA, Norway, Iceland and Liechtenstein. According to Article 2 of Regulation (EC) No 726/2004, the marketing authorization holder must be established in the EEA. This means for the UK that as of the end of the transition period (end of 2020), a marketing authorization holder currently established in the

UK has to have transferred its marketing authorization to a holder established in the EEA. The transfer of the marketing authorization must be fully completed and implemented by the marketing authorization holder before the end of the transition period. Also, any application for marketing authorizations must be made by applicants established in the EEA. Therefore, applications made by applicants established in the UK will need to change to an applicant established in the EEA.

Under the centralized authorization procedure, the EMA's Committee for Medicinal Products for Human Use, or CHMP, serves as the scientific committee that evaluates applications and renders opinions about the safety, efficacy and quality of human products on behalf of the EMA. The CHMP is composed of experts nominated by the Competent Authority of each European Union Member State, one of which is appointed to act as rapporteur for the coordination of the evaluation with the possible assistance of a further member acting as a co-rapporteur. The CHMP has 210 days to give its opinion to the EMA as to whether a marketing authorization should be granted. This period will be suspended until such time as the supplementary information requested by the CHMP has been provided by the applicant. Likewise, this time-limit will be suspended for the time allowed for the applicant to prepare oral or written explanations. The evaluation process is complex and involves extensive consultation with the Competent Authorities of the Member States of the European Union and a number of experts. It is possible to appeal the opinion within 15 days of receipt of the notification of the opinion. At the end of the re-examination, which lasts up to 60 active days, the CHMP adopts a final opinion. The European Commission usually takes its decision to grant a legally binding authorization within 67 days after obtaining the CHMP decision.

A marketing authorization that has been granted in the European Union may be suspended or withdrawn if ongoing regulatory requirements are not met or if safety problems are identified. Among other things, marketing authorization holders are required to have risk management plans that use risk minimization strategies beyond product labelling to ensure that the benefits of certain prescription drugs outweigh their risks.

Accelerated Assessment Procedures

When an application is submitted for a marketing authorization in the European Union in respect of drugs for human use which is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure pursuant to Article 14 (9) of Regulation (EC) No. 726/2004, as amended. Based on the request, the justifications presented, and the recommendations of the rapporteurs, the CHMP will formulate a decision. Such a decision will be taken without prejudice to the CHMP opinion (positive or negative) on the granting of a marketing authorization. If the CHMP accepts the request, the timeframe for the evaluation will be reduced from the standard 210 days for the centralized procedure to 150 days, but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment.

Conditional Marketing Authorization and Authorization under Exceptional Circumstances

A conditional marketing authorization is valid for one year, can be renewed annually and may be requested by an applicant or proposed by the CHMP for medicinal products which aim at:

- the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases;
- medicinal products to be used in emergency situations in response to public health threats recognized either by the World Health Organization or by the European Union in the framework of Decision No. 1082/2013/EU (e.g. COVID-19 treatments); or
- medicinal products designated as orphan medicinal products in accordance with Regulation (EC) No. 141/2000, as amended.
- A conditional marketing authorization may be requested by an applicant or proposed by the CHMP for medicinal products if all of the following requirements are met:
- the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, as amended, is positive;
- it is likely that the applicant will be in a position to provide comprehensive clinical data;
- unmet medical needs will be fulfilled (no existing satisfactory methods or the medicinal product provides major therapeutic advantage); and
  the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

The legal basis for a conditional marketing authorization is Article 14-a of Regulation (EC) No. 726/2004, as amended. The provisions for the granting of such an authorization are further elaborated in Regulation (EC) No. 507/2006. The holder will be required to complete ongoing studies or to conduct new studies within a specified period of time with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

In addition, authorization under exceptional circumstances may be requested when it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence;
- in the present state of scientific knowledge, comprehensive information cannot be provided; or
- it would be contrary to generally accepted principles of medical ethics to collect such information.

The legal basis for the marketing authorization under exceptional circumstances is Article 14 (8) of Regulation (EC) No. 726/2004, as amended, and the relevant documentation for applications in exceptional circumstances are laid down in Part II of Annex I of Directive 2001/83/EC, as amended. The authorization under exceptional circumstances is granted subject to a requirement for the applicant to meet certain conditions, in particular concerning the safety of the medicinal product, notification to the Competent Authorities of any incident relating to its use, and action to be taken. The renewal of the marketing authorization of a medicinal product under exceptional circumstances follows the same rules as a "normal" marketing authorization. After five years, the marketing authorization will then be renewed under exceptional circumstances for an unlimited period, unless the Competent Authority decides on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.

Manufacturing and Manufacturers' Authorization

Directive 2003/94/EC, as amended, requires that the manufacturing of investigational medicinal products and approved drugs in the EEA is subject to a separate manufacturing authorization and must be conducted in strict compliance with GMP requirements, which mandate the methods, facilities, and controls used in manufacturing, processing, and packing of drugs to assure their safety and identity. Manufacturers must have at least one Qualified Person, or QP, permanently and continuously at their disposal. Although the ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality, and efficacy, lies with the marketing authorization holder, the QP is responsible for ensuring that each batch of finished product released onto the market has been manufactured in accordance with GMP, in compliance with EU laws and the specifications set out in the marketing authorization or investigational medicinal product dossier. Certification can only be performed by a QP of the manufacturer and/or importer, which are described in the marketing authorization. GMP requirements are enforced through mandatory registration of facilities and inspections of those facilities. Failure to comply with these requirements could interrupt supply and result in delays, unanticipated costs, and lost revenues, and subject the applicant to potential legal or regulatory action, including but not limited to warning letters, suspension of manufacturing, seizure of product, injunctive action, or possible civil and criminal penalties.

Commercialization and Promotion

The commercialization and promotion of authorized medicinal products, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs, are strictly regulated in the European Union, notably under, among others, Directive 2001/83/EC, as amended, guidance published by the European Commission and the EMA, laws, regulations and guidance set out by the Member States of the European Union and industry wide codes of conduct. The applicable regulatory framework aims to ensure that information provided by holders of marketing authorizations regarding their products is truthful, balanced and accurately reflects the safety and efficacy claims authorized by the EMA or by the Competent Authority of the authorizing Member State. Failure to comply with these requirements can result in adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Commercialization and promotion of prescription only medicinal products to consumers or patients (directly or indirectly) is strictly forbidden. Advertising of medicines pre-approval or off-label is also prohibited.

Regulatory Data Protection and Market Exclusivity

In the European Union, all new active substances approved on the basis of a complete independent data package benefit from an 8+2+1 year data/market exclusivity regime. This regime consists of (i) a regulatory data protection period and market exclusivity period of eight years, (ii) a market exclusivity period of an additional two years after the eight-year period and (iii) an extended market exclusivity period of one year after the 10-year period if, during the first eight years of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications which, during the scientific evaluation prior to their approval, are determined to bring a significant clinical benefit in comparison with existing therapies. Under the current rules, a third party may reference the preclinical and clinical data of the original innovator beginning eight years after

notification of the grant of the approval in the European Union, but the third party may market a generic version after only 10 or, where applicable, 11 years have lapsed from the notification of the grant of the approval.

Orphan Designation

Medicines that meet the criteria for orphan designation benefit from the incentive of 10 years of market exclusivity once they are approved for commercialization in the European Union. This protects them from market competition with similar medicines with the same indication once they are approved. Market exclusivity is awarded by the European Commission and is specifically linked to one specific orphan designation for which a marketing authorization has been granted. Each orphan designation carries the potential for one market exclusivity for a particular indication. A medicine that has several separate orphan designations for different indications can have several separate market exclusivities if these refer to separate designated conditions. A designated orphan medicinal product shall be removed from the European Union's Community register of orphan medicinal products at the end of the period of market exclusivity.

The period of market exclusivity is extended by two years for medicines that also have complied with an agreed pediatric investigational plan, or PIP. This period may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation, including among other things, if the product is sufficiently profitable so that market exclusivity is no longer justified.

Notwithstanding the foregoing, a marketing authorization may be granted, for the same therapeutic indication, to a similar drug if:

- the holder of the marketing authorization for the original orphan drug has given its consent to the second applicant;
- the holder of the marketing authorization for the original orphan drug is unable to supply sufficient quantities of the drug; or
- the second applicant can establish in the application that the second drug, although similar to the orphan drug already authorized, is safer, more effective or otherwise clinically superior.

Regulation (EC) No 847/2000 lays down definitions of the concepts "similar drug" and "clinical superiority."

In order to be eligible for incentives made available by the European Union and by the Member States to support research into, and the development and availability of, orphan drugs, the medicinal product needs to be designated as an orphan drug pursuant to Regulation (EC) No. 141/2000, as amended. Regulation (EC) No. 141/2000, as amended, states that a medicinal product shall be designated as an orphan medicinal product if its manufacturer can establish:

- that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union when the application is made or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the European Union

and that without incentives it is unlikely that the commercialization of the medicinal product in the European Union would generate sufficient return to justify the necessary investment; and

- that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the community or, if such method exists, the medicinal product will be of significant benefit to those affected by that condition.

Small- or Medium-Sized Enterprise Status

In the European Union, manufacturers may benefit from further incentives, including administrative and procedural assistance and fee reductions when they are classified as a small- or medium-sized enterprises, or SME. Within the SMEs, medium enterprises are defined as those which employ between 50 to 249 persons and which have an annual turnover not exceeding €50 million or an annual balance sheet total not exceeding €43 million; a small enterprise is defined as an enterprise which employs between 10 to 49 persons and whose annual turnover or annual balance sheet total does not exceed €10 million; and a microenterprise is defined as an enterprise which employs fewer than 10 persons and whose annual turnover or annual balance sheet total does not exceed €2 million.

Administrative, regulatory and financial support is available to companies assigned the SME status by the EMA, including:

- direct assistance by phone, email, teleconference or through briefing meetings on regulatory aspects of the pharmaceutical legislation;
- fee exemptions and reductions for pre- and post-authorization regulatory procedures, including scientific advice, inspections and pharmaco-vigilance;
- assistance with translations of product information into all official European Union languages;
- inclusion in an online SME register, which is an important source of information on the EU-based SMEs involved in the manufacturing, development or marketing of medicines and promotes partnering and networking between the SMEs;
- guidance on clinical data publication and a free redaction tool license;
- liaison with academic investigators in pediatric-medicine research through the European Network of Pediatric Research at the EMA; and
- workshops and training sessions.

Development of Medicines for Children

Several incentives for the development of medicines for children are available in the European Union:

- medicines that have been authorized across the European Union with the results of PIP studies included in the product information are eligible for an extension of their patent protection by six months even when the studies' results are negative;
- for orphan medicines, the incentive is an additional two years of market exclusivity;
- scientific advice and protocol assistance at the EMA are free of charge for questions relating to the development of medicines for children; and

- medicines developed specifically for children that are already authorized but are not protected by a patent or supplementary protection certificate, can apply for a pediatric-use marketing authorization, or PUMA, which provides 10 years of market protection.

Pediatric Regulation

On January 26, 2007, the Pediatric Regulation (Regulation (EC) No. 1901/2006 and Regulation (EC) No. 1902/2006) came into force in the European Union. Its objective is to improve the health of children in the European Union by facilitating the development and availability of medicines for children from birth up to 18 years of age, ensuring that medicines for use in children are of high quality, ethically researched and authorized appropriately and improving the availability of information on the use of medicines for children. The aim is to achieve this without subjecting children to unnecessary trials or delaying the authorization of medicines for use in adults. The Pediatric Regulation established the Pediatric Committee, or PDCO, which is responsible for coordinating the EMA's work on medicines for children. The Committee's main role is to determine the studies that companies must carry out on children as part of PIPs. At least an approved PIP needs to be in place before applying for marketing authorization. The PDCO grants deferrals for some medicines, allowing a company to delay development of the medicine in children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO also grants waivers when development of a medicine in children is not needed or is not appropriate, such as for diseases that only affect the elderly population. When the approved PIP contains studies that need to be performed, the proposed study design and timelines need to be adhered to.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we obtain regulatory approval. Countries have different pricing and reimbursement schemes. In the European Union, the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage and establish adequate reimbursement levels for such products.

In the European Union, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines but monitor and control company profits. Special pricing and reimbursement rules may apply to orphan drugs. Inclusion of orphan drugs in reimbursement systems tends to focus on the medical usefulness, need, quality and economic benefits to patients and the healthcare system as for any drug. The downward pressure on health care costs has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

In the United States, third-party payors include federal and state healthcare programs, private managed care providers, health insurers and other organizations. Even if our product candidates are

approved, sales of our products will depend, in part, on the extent to which third-party payors provide coverage and establish adequate reimbursement levels for such products. The process for determining whether a third-party payor will provide coverage for a product may be separate from the process for setting the price of a product or for establishing the reimbursement rate that such a payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the FDA-approved products for a particular indication. Third-party payors are increasingly challenging the price, examining the medical necessity and reviewing the cost-effectiveness of medical products, therapies and services, in addition to questioning their safety and efficacy. We may need to conduct expensive pharmaco-economic studies in order to demonstrate the medical necessity and cost-effectiveness of our product candidates, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

In addition, prices for drugs may be reduced by mandatory discounts or rebates required by federal health care programs (such as the Medicaid Drug Rebate Program and the 340B Drug Pricing Program) or discounts and rebates requested by private payors. In addition, any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States may also impact the pricing of drugs. It is difficult to predict how Medicare coverage and reimbursement policies will be applied to products for which the company receives marketing approval in the future and coverage and reimbursement under different federal health care programs is not always consistent. Further, private payors often follow the coverage and reimbursement policies established under Medicare. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our products for which we receive marketing approval.

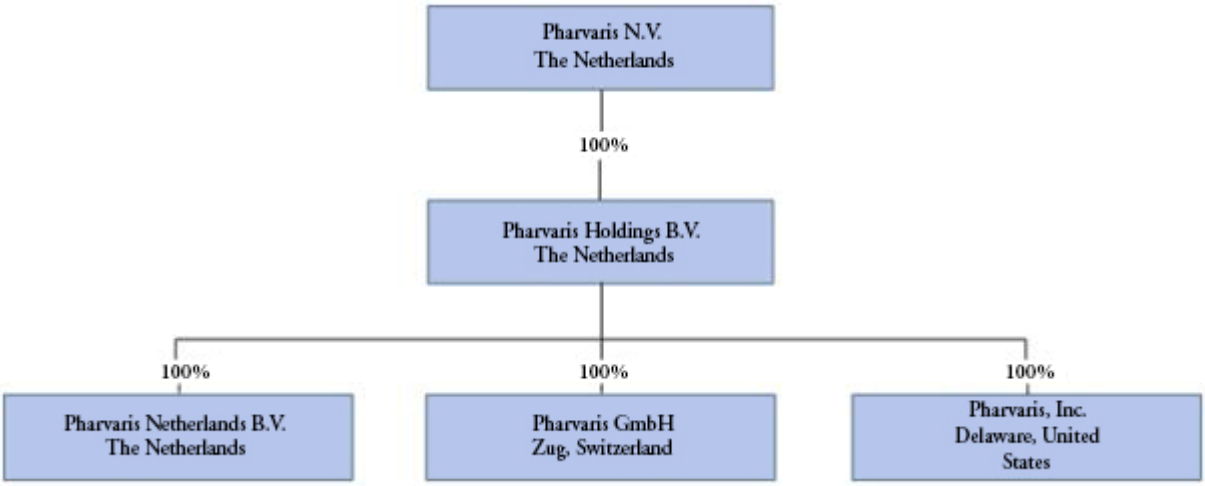
The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

The marketability of any product candidates for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on healthcare pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

2.3 Organizational Structure

We are incorporated as a Dutch public company with limited liability (*naamloze vennootschap*) with operating subsidiaries in the Netherlands, Switzerland and the United States.

The following diagram illustrates our corporate structure:



2.4 Property, plants and equipment

We have offices in Waltham, Massachusetts; Zug, Switzerland; and Leiden, The Netherlands. Our office space in Massachusetts measuring approximately 25.5 square meters is rented on a monthly basis; our office space in Switzerland measuring approximately 13 square meters is rented on an annual basis; and our office space in the incubator at the Bioscience Park in Leiden measuring approximately 216.5 square meters is sub-leased on a yearly basis.

2.5 Operating results

You should read the following discussion of our financial condition and results of operations in conjunction with the consolidated financial statements included in the "**Consolidated Financial Statements**" and the notes included elsewhere in this report. The following discussion contains forward-looking statements that involve certain risks and uncertainties. Our actual results could differ materially from those discussed in these statements. Factors that could cause or contribute to these differences include those discussed below and elsewhere in this report, particularly under chapter 3.2 and chapter 1.2.

Our audited consolidated financial statements are included elsewhere in this report. These consolidated financial statements are prepared pursuant to IFRS as adopted by the European Union.

Financial operations overview

Revenues

We did not record any revenues during the period covered by the historical financial information included in this report. We do not expect to recognize any revenues before we are able to commercialize our first product.

Research and development expenses

We are focused on the clinical development of PHA121. Since our inception, we have devoted substantially all of our resources to research and development efforts relating to the development of PHA121 and our product candidates PHVS416 and PHVS719. We expect that we will continue to incur significant research and development expenses as we seek to complete the clinical development of, and achieve regulatory approval for, our product candidates PHVS416 and PHVS719, and in connection with discovery and development of any additional product candidates.

Research and development expenses consist of the following:

- employee benefits expenses, which includes salaries, pensions, share-based compensation expenses, bonus plans and other related costs for research and development staff;
- pre-clinical expenses, which include costs of our outsourced discovery, preclinical and nonclinical development studies;
- clinical expenses, which includes costs of conducting and managing our sponsored clinical trials, including clinical investigator cost, costs of clinical sites, and costs for CRO's assisting with our clinical development programs;
- manufacturing expenses, which include costs related to manufacturing of active pharmaceutical ingredients and manufacturing of the products used in our clinical trials and research and development activities;
- costs related to regulatory activities, including collecting data, preparing and submitting filings, communicating with regulatory authorities and reviewing the design and conduct of clinical trials for compliance with applicable requirements;
- costs in connection with investigator-sponsored clinical trials and evaluations;
- advisers' fees, including discovery, nonclinical, clinical, chemistry, manufacturing, and controls- related and other consulting services;
- intellectual property costs, which includes costs associated with obtaining and maintaining patents and other intellectual property; and
- license costs.

We anticipate that research and development expenses will continue to increase as we continue to progress PHVS416 and PHVS719 through clinical development.

There is a risk that any clinical development or product discovery program may not result in commercial approval. To the extent that we fail to obtain approval to commercialize our product candidate in a timely manner, we would need to continue to conduct clinical trials over a longer period of time, and we anticipate that our research and development expenses may further increase.

Clinical development timelines and associated costs may vary significantly and the successful development of our product candidate is highly uncertain. At this time, we cannot reasonably estimate the nature, timing and estimated costs of the efforts, including patient recruitment and selection that will be necessary to complete the development of, or the period, if any, in which material net cash inflows may commence from, our product candidates. Moreover, we cannot assure that we will be able to successfully develop or commercialize our product candidates, if approved for marketing. This is due to numerous risks and uncertainties associated with developing drugs. See chapter 3.2.

Selling and distribution expenses

Historically, we have not incurred any selling and distribution expenses. If our product candidates are approved for registration and marketing, we anticipate incurring substantial selling and distribution expenses in future periods in order to establish an infrastructure for marketing and distribution, obtain supplies of active pharmaceutical ingredients, and manufacture commercial quantities of our product candidate.

General and administrative expenses

We anticipate that we will continue to incur significant general and administrative expenses as we advance our research and development portfolio. General and administrative expenses consist of the following:

- employee benefits, including salaries, pensions, share-based compensation expenses, bonus plans and other related costs for staff and independent contractors in executive and operational functions;
- auditors' and advisers' fees, including accounting, tax, legal and other consulting services; and
- rental expenses, facilities and IT expenses and other general expenses relating to our operations.

We anticipate that the continuing development of our business and the expense of maintaining directors' and officers' liability insurance, will contribute to future increase in general and administrative expenses. We also expect that general and administrative expenses will increase in the future as we incur additional costs associated with being a public company in the United States.

Share-based compensation expenses

In 2016, we implemented an Equity Incentive Plan, or the Plan, in order to advance the interests of our shareholders by enhancing our ability to attract, retain and motivate persons who are expected to make important contributions to us and by providing such persons with performance-based incentives that are intended to better align the interests of such persons with those of our shareholders. The fair value of these instruments are recognized as personnel expenses in either research and development and expense. The plan has been superseded by the 2021 Long Term Incentive plan after completion of the IPO in February 2021.

Comparison of the years ended December 31, 2019 and 2018

A discussion of the financial results for the year ended December 31, 2019 as compared to the year ended December 31, 2018 can be found in the section entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations" in our registration statement on Form F-1 (Registration No. 333-252157) filed with the SEC.

Comparison of the years ended December 31, 2020 and 2019

The following table summarizes our loss for the periods indicated:

	2020	2019
	€	€
Research and development expenses	(19,508,101)	(5,684,562)
General and administrative expenses	(5,498,491)	(2,325,719)
Total operating expenses	(25,006,592)	(8,010,281)
Finance expenses	(1,062,363)	(16,881)
Loss before income tax	(26,068,955)	(8,027,162)
Income tax benefit	83,251	-
Loss for the year	(25,985,704)	(8,027,162)

Research and development expenses

	2020	2019
	€	€
Personnel expenses (Note 5)	(2,951,323)	(131,544)
Clinical expenses	(8,748,748)	(2,009,892)
Pre-clinical expenses	(3,322,590)	(1,850,444)
Manufacturing costs	(4,311,958)	(1,379,590)
License costs	-	(300,000)
Intellectual Property costs	(173,482)	(13,092)
	(19,508,101)	(5,684,562)

Research and development expenses increased by €13,823,539 in 2020, or 243% from €5,684,562 for the year ended December 31, 2019 to €19,508,101 for the year ended December 31, 2020. The increase in research and development expenses was primarily due to the expansion of the Phase 1 clinical program in 2020, the progression of preclinical studies to prepare for the Phase 2 clinical program, and the start of our Phase 2 clinical program in 2020. The cost of manufacturing of PHA121 for preclinical and clinical studies, and expanded formulation development work were also major cost drivers in 2020. In personnel expenses, an amount of €1,215,937 for 2020 and €99,946 for 2019 is related to the share-based compensation arrangements. The increase in personnel expenses was primarily due to the stock options granted to the Board and our Senior Management in 2020. In 2019, a

milestone payment of €300,000 was paid to AnalytiCon upon commencement of Phase 1 development.

General and Administrative Expenses

	2020	2019
	€	€
Personnel expenses (Note 5)	(1,490,674)	(49,601)
Consulting fees	(1,042,195)	(990,730)
Professional fees	(943,322)	(495,326)
Accounting, tax and auditing fees	(1,275,842)	(300,841)
Travel expenses	(26,773)	(236,904)
Facilities, communication & office expenses	(551,223)	(167,062)
Other expenses	(168,462)	(85,255)
	(5,498,491)	(2,325,719)

General and administrative expenses increased by €3,172,772, or 136% from €2,325,719 for the year ended December 31, 2019 to €5,498,491 for the year ended December 31, 2020. The increase in general and administrative expenses was mainly driven by the growth of the Group and the associated engagement of consultants and service providers as well as the hiring of additional employees to support the Group's activities and to fulfil legal, tax and reporting compliance requirements. In addition, the Group's preparation for an initial public offering led to an increase in legal, accounting and reporting expenses. In personnel expenses, an amount of €371,799 for 2020 and €16,201 for 2019 is related to the share-based compensation arrangements.

Finance expenses

Our finance expenses increased by €1,045,482 from €16,881 for the year ended December 31, 2019 to €1,062,363 for the year ended December 31, 2020. This increase is due to the translation of the Group's bank balances in foreign currency into the Group's reporting currency and the increase in the services rendered from parties invoicing in a currency different to the Group reporting currency.

Income taxes

We have a history of losses. The tax benefit over the year ended December 31, 2020 relates to a temporary difference in the Company's US subsidiary for which a deferred tax asset is recognized, partly offset by the current tax charges relating to the Company's US subsidiary as the result of a cost-plus agreement between the US entity and Group's principal entity resulting in a taxable profit in the United States of America. We have not recognized deferred tax assets relating to losses carried forward for the Company's Dutch and Swiss entities for approximately €43.3 million (2019: €5.9 million). These losses carried forward are available for offsetting against future taxable profits of the companies in which the losses arose. Under Dutch tax law, for years prior to 2019, profits in a given year can be offset against tax loss carry forwards for up to nine years. In 2019, the Dutch tax law was revised to limit the carry forward period to six years. Under Swiss law, losses can be offset against future income or capital gains for seven years.

Critical accounting estimates and judgments

We believe that the following accounting policies involve a high degree of judgment and complexity. Accordingly, these are the policies we believe are the most critical to aid in fully understanding and evaluating our consolidated financial condition and results of our operations. See Note 2 to our consolidated financial statements included elsewhere in this report for a description of our other significant accounting policies. The preparation of our consolidated financial statements in conformity with IFRS requires us to make estimates and judgments that affect the amounts reported in those financial statements and accompanying notes. Although we believe that the estimates we use are reasonable, due to the inherent uncertainty involved in making those estimates, actual results reported in future periods could differ from those estimates.

Share-based Compensation Arrangements

We adopted an equity-settled share-based compensation plan in 2016, pursuant to which certain participants are granted the right to acquire ordinary shares or RSU's of the Company. The grants made under this plan are accounted for in accordance with the policy as stated in Note 2.14 to our consolidated financial statements included elsewhere in this report. The total amount to be expensed is determined by reference to the fair value of the options or RSUs granted.

Due to the lack of quoted market prices, we have determined the fair value for the measurement of the equity-settled transactions at the grant date with assistance of an external appraiser, considering certain assumptions relating to the volatility of stock price, the determination of an appropriate risk-free interest rate and expected dividends.

We consider numerous objective and subjective factors to determine the best estimate of the fair value of the ordinary shares as of each grant date, including:

- the progress of the research and development programs;
- contemporaneous third-party valuations of the ordinary shares for the share issuances in 2016, 2019 and 2020;
- the rights and preferences of the preferred shares relative to the ordinary shares;
- the likelihood of achieving a discrete liquidity event, such as a sale of the company or an initial public offering given prevailing market conditions; and
- external market and economic conditions impacting the industry sector.

The fair value of an option or an RSU was measured based on the estimated fair value of an ordinary shares at grant date. An external valuation expert has estimated the fair value of the Company's ordinary shares, on a minority basis, as of the grant dates based on the pricing of the most recent financing round of the Company at the time. As we were a private company and the equity instruments were not marketable, an Option Pricing Model, with estimated probabilities of two different exit scenarios (IPO and Trade Sale), was applied to back-solve the Company's total equity value such that the value per Series B preferred share and Series C preferred shares is equal to the investment price per share paid in the investment round.

This estimated total equity value has been used as input to the Option Pricing Model when determining the fair value of the Company's ordinary shares at the grant/measurement dates. The Option Pricing Model uses the Black-Scholes Option-Pricing Model to determine the fair value of the

Company's different share classes based upon the Company's total equity value.

The inputs used in the measurement of the fair value per ordinary share at each grant/ measurement date based upon the total equity value were as follows:

	December 31, 2020	December 17, 2020	July 13, 2020	February 3, 2020	January 1, 2020
Expected volatility (%)	90%	90%	90%	80%	80%
Expected life (years)	1.6	1.6	1.6	3.0	3.0
Risk-free interest rate (%)	-0.8%	-0.8%	-0.8%	-0.6%	-0.6%
Expected dividend yield	-	-	-	-	-

The input used in the measurement of the fair value per option at each grant/measurements date using the Black-Scholes formula (including the related number of options and the fair value of the options) were as follows:

	December 31, 2020	December 17, 2020	July 13, 2020	February 3, 2020	January 1, 2020
Number of options	88,000	32,445	44,000	308,000	600,000
Fair value of the options	€6.08	€5.07	€4.74	€1.66	€1.67
Fair value of the ordinary shares	€7.25	€7.25	€5.82	€2.38	€2.38
Exercise price	€2.38	€7.25	€2.38	€2.38	€2.38
Expected volatility (%)	85%	85%	85%	85%	85%
Expected life (years)	6.1	6.1	6.0	6.1	6.1
Risk-free interest rate (%)	-0.6%	-0.7%	-0.6%	-0.6%	-0.4%
Expected dividend yield	-	-	-	-	-

Expected volatility was based on an evaluation of the historical volatilities of comparable listed biotech-companies over the most recent historical period that commensurate with the expected option life. The expected life is based on Management's best estimate of when the options will be exercised. The risk-free interest rate is based on the yield on German government Strip bonds, with tenure equal to the expected life. The expected dividend yield is zero considering the stage of the Company.

On March 31, 2016 the Company has granted 392,850 stock options to a consultant, with an exercise price of €0.01. The estimated fair value of the stock options at grant date was €1.24. On December 13, 2018 a total of 25,295 restricted stock units were granted to a consultant. The purchase price is €0.01 and the estimated fair value at the grant date was €1.39.

On January 1, 2020 the Company has granted a total of 600,000 stock options to members of our Senior Management with an exercise price of €2.38 per share with a final exercise date of December 31, 2029 unless forfeited or exercised on an earlier date.

On February 3, 2020, we granted 308,000 stock options to a member of our Senior Management with an exercise price of €2.38 per share. Also on February 3, 2020, we granted 132,000 stock options to a member of Senior Management with an exercise price of €2.38 per share, these options in addition to the service condition also include a performance condition. On July 13, 2020 the performance goals for 2020 were determined and the fair value of the related options was reassessed for the options subject to the performance goals for 2020. The fair value of the stock options related to the performance periods 2021 and 2022 was reassessed on December 31, 2020.

On December 17, 2020 a total of 32,445 options were granted to employees with an exercise price of €7.25 per share. On December 17, 2020 a total of 128,300 RSUs were granted to employees.

The fair value of the RSUs of €9.67 is determined based on the share value per ordinary share at the grant date, prior to applying a discount for lack of marketability.

Research and development expenditures

Research and development expenses are currently not capitalized but are expensed because the criteria for capitalization are not met, see Note 2.15 and Note 4 in our consolidated financial statements included elsewhere in this report. At each balance sheet date, we estimate the level of services performed by the vendors and the associated costs incurred for the services performed. Although we do not expect the estimates to be materially different from amounts actually incurred, the understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in reporting amounts that are too high or too low in any particular period.

Liquidity and capital resources

Since inception, we have incurred significant operating losses. We incurred losses of €8,027,162 during the year ended December 31, 2019 and €25,985,704 during the year ended December 31, 2020. Since inception, we have not generated any revenues or net cash flows from sales. We will not receive any revenues or net cash flows from sales until we successful develop a product candidate, obtain regulatory approval and successfully commercialize it. There is no assurance that we will be able to do so.

To date, we have relied solely on the issuance of equity securities to finance our operations and internal growth. From inception through December 31, 2020, we have raised the following capital:

- issuance of 4,850,000 Common shares raising €225,000;
- issuance of 5,242,850 Series A preferred shares raising €14,899,133 (net of transaction costs); and
- issuance of 3,003,391 Series B-1 preferred shares raising €21,631,526 (net of transaction costs).
- issuance of 4,646,756 Series B-2 preferred shares raising €34,246,281 (net of transaction costs).
- issuance of 5,826,279 Series C preferred shares raising €67,183,593 (net of transaction costs).

As of December 31, 2020 we held cash and cash equivalents of €98,628,871. We expect that the net proceeds (after deducting underwriters'discount)of $176.9 million from our initial public offering, together with our existing cash, will enable us to fund our operating expenses and capital expenditure requirements for at least the next 24 months.

We have based our estimate on assumptions that may prove to be wrong, and we may use our available capital resources sooner than we currently expect. For example, we may require additional capital resources due to underestimation of the nature, timing and estimated costs of the efforts that will be necessary to complete the development of our product candidates. We may also need to raise additional funds more quickly if we choose to expand our development activities, our portfolio or if we consider acquisitions. Factors that could influence our future capital requirements and the timing thereof include:

- the progress and cost of our discovery, preclinical and nonclinical development;

- the progress and cost of our clinical trials, including payments of patient and clinical site cost, clinical investigator cost and payments to CROs that are assisting with our sponsored clinical trials, and other research and development activities;
- the cost and timing of obtaining regulatory approval to commence further clinical trials;
- the costs associated with any future investigator-sponsored clinical trials;
- the cost of filing, prosecuting, defending and enforcing any patent applications, claims, patents and other intellectual property rights;
- the cost and timing of obtaining sufficient quantities of our product candidates for clinical trials by establishing our contracted and/or own production capacities;
- the terms and timing of any collaborative, licensing and other arrangements that we may establish;
- the costs of any delays caused by the COVID-19 pandemic and associated restrictions;
- the cost of preparing for launch and commercialization of our product candidate; and
- the cost of operating as a public company in the United States.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings, convertible loans, warrants, collaborations or other means. We may consider raising additional capital to take advantage of favorable market conditions or other strategic considerations even if we have sufficient funds for planned operations.

To the extent that we raise additional funds by issuing and selling equity or equity-linked securities, shareholders will experience dilution. Debt financings, if available, may subject us to financial and other restrictive covenants that limit our ability to engage in activities that we may believe to be in our long-term best interests. Additional financing may not be available on acceptable terms, if at all. Capital may become difficult or impossible to obtain due to poor market or other conditions outside of our control (including the COVID-19 pandemic). If we are unable to raise additional funds when needed, we may be required to delay, reduce, or terminate some or all of our development programs and clinical trials. We may also be required to sell or license to others, technologies or our clinical product candidate that we would prefer to develop and commercialize ourselves.

Cash Flows

Comparison for the years ended December 31, 2020 and December 31, 2019

The following table sets forth our primary sources and uses of our cash and cash equivalents for each of the periods set forth below:

	For the year ended December 31,			
	2020	**2019**	**Change**	**%**
		(in €)		
Net cash flows used in operating activities	(21,499,593)	(6,677,011)	(14,822,582)	222%
Net cash flows used in investing activities	(42,977)	(13,476)	(29,501)	219%
Net cash flows provided by financing activities	101,200,801	21,631,526	79,569,275	368%

	For the year ended December 31,			
	2020	2019	Change	%
		(in €)		
Net increase in cash and cash equivalents	**79,658,231**	**14,941,039**	**64,717,192**	**433%**
Cash and cash equivalents at beginning of period	**20,326,372**	**5,385,333**	**14,941,039**	**277%**
Effect of exchange rate changes	(1,355,732)	-	(1,355,732)	100%
Cash and cash equivalents at end of period.....	**98,628,871**	**20,326,372**	**78,302,499**	**385%**

Operating activities

Net cash flows used in operating activities reflects our results for the period adjusted for, among other things, depreciation, unrealized foreign exchange results, share-based compensation arrangements, changes in working capital and accruals.

Net cash flows used in operating activities increased by €14,822,582 or 222%, from €6,677,011 for the year ended December 31, 2019 to €21,499,593 for the year ended December 31, 2020, primarily reflecting the increase in costs related to outsourced preclinical, clinical development activities and manufacturing of PHA121, financing activities and the accompanying growth of the Company, in particular with respect to the increase in personnel and accounting, tax and audit fees.

Investing activities

Net cash flows used in investing activities increased by €29,501 or 219%, from €13,476 for the year ended December 31, 2019 to €42,977 for the year ended December 31, 2020, primarily as a result of capital expenditures for office equipment as a result of the increase in personnel and the number of offices rented.

Financing activities

Net cash flows provided by financing activities increased by €79,569,275, or 368%, from €21,631,526 for the year ended December 31, 2019 to €101,200,801 for the year ended December 31, 2020 primarily as the result of net proceeds of €34,246,281 from the Series B preferred shares and €67,183,593 from the Series C preferred shares issued in July and November 2020 respectively.

Outlook

The outlook on our business is described in the "Business" section of this report.

We will hire additional employees when necessary, to support the Group's activities and to fulfil legal, tax and reporting compliance requirements.

We expect that the net proceeds of $176.9 million from our initial public offering, together with our existing cash, will enable us to fund our operating expenses and capital expenditure requirements

for at least the next 24 months.

2.6 Material subsequent events

On January 1, 2021 Mr. M.E. Rome resigned as member of the Board. On the same date the shareholders approved the appointment of Mr. D. Meeker and Mr. R. Glassman as members of the Board and a grant of 107,000 stock options were approved by the Board, with an exercise price of €7.25 per stock option.

On February 5, 2021, the Company's ordinary shares began trading on the Nasdaq Stock Exchange. On the same date the Company converted from a Dutch private company with limited liability (B.V.) into a Dutch public limited liability company (N.V.).

On February 5, 2021, a grant of 873,000 stock options was approved by the Board, with an exercise price equal to the issue price of the shares.

On February 9, 2021, the Company completed its IPO. The total gross raised from the IPO were USD 190.2 million and the total net proceeds raised from the IPO, after deducting underwriting discounts, were USD 176.9 million.

On May 1, 2021, Dr. R. Gaster resigned as member of the Board.

On May 12, 2021, the Company announced the expansion of their leadership team through the appointment of Dr W. Souverijns, as Chief Community Engagement & Commercial Officer.

On May 26, 2021, the Company announced that the Board has nominated Ms. V. Monges to be appointed to the Board by the General Meeting at the Company's annual general meeting 2021 contingent on her appointment by the General Meeting, Ms V. Monges will also become the Chair of the Audit Committee.

See Note 23 (*Events after the reporting period*) to the consolidated financial statements for a further overview of events which do not need to be discussed in the Company's statutory annual accounts and which might influence the Company's outlook.

There are no other events which might influence the Company's outlook and which are not discussed in the statutory annual accounts included in this report.

3 RISK FACTORS

3.1 Summary of key risk factors

The principal risks and uncertainties which the Company faces include the risks and uncertainties summarized in this chapter 3.1. See chapter 3.2 of this report for additional detail and additional risks and uncertainties which the Company faces.

- We have a limited operating history, have generated no revenues to date and have incurred significant losses since our inception. We expect to incur losses over the next several years, will not generate revenues until we are able to commercialize our products and may never achieve profitability, while our net losses are expected to fluctuate significantly.
- If we are unable to raise capital when needed or on acceptable terms, we may need to delay, reduce or terminate our product development programs and may be unable to continue as a going concern and could ultimately go into insolvency.
- Our business and operations may be adversely affected by a variety of events outside our control, including, but not limited to, pandemics, epidemics or outbreaks of infectious diseases such as the recent COVID-19 pandemic.
- We are heavily dependent on the success of our product candidates PHVS416 and PHVS719, which are in early stage development and have not yet been assessed for efficacy in a clinical trial. We cannot give any assurance that either product candidate, or any other compounds in development, will successfully complete clinical trials, receive regulatory approval, be commercialized, or be differentiated in the market. If we are unable to successfully commercialize our product candidates, or experience significant delays in doing so, our business, financial condition, results of operations and prospects would be materially adversely affected.
- We may experience setbacks in our clinical trials, including delays in commencing, conducting or completing our clinical trials. Moreover, we have established proof-of-mechanism for PHA121 and have designed and advanced our future clinical development program based on a clinical trial that assessed a surrogate assessment, as well as modelling of our results from that trial with additional in vitro and in vivo data and comparisons to published results for other currently available products from different trials. We may not be able to replicate these results or analyses in future clinical trials that assess the endpoints required to obtain regulatory approval or we may have inconclusive or negative results. Any setbacks in our clinical development program could have a material adverse effect on our business, financial condition, results of operations and prospects.
- Clinical trials of our product candidates may not uncover all possible adverse effects that patients may experience.
- There can be no assurance that we will be able to obtain or, if obtained, maintain orphan drug status.
- We have identified material weaknesses in our internal control over financial reporting. If we are unable to successfully remediate these material weaknesses and to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud, and as a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our ordinary shares.

- We and our partners may be subject to new legislation, regulatory proposals and healthcare payor initiatives that may increase our costs of compliance and adversely affect our or our partners' ability to market our products, obtain collaborators and raise capital.
- Manufacturing issues may arise that could increase product and regulatory approval costs or delay commercialization of our products.
- The market opportunities for our product candidates may also be smaller than currently anticipated, lowering our potential revenue.
- If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products. This may make it difficult for us to achieve our business strategy of using our product candidates in combination with existing therapies or replacing existing therapies with our product candidates.
- Governments and/or pricing authorities, especially in the European Union, often impose strict price and access controls, which may adversely affect our future profitability.
- The insurance coverage and reimbursement status of newly approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current products could limit our ability to market those products and decrease our ability to generate revenue.
- We may become exposed to costly and damaging liability claims, either when testing our product candidates in the clinic or after commercialization; and our product liability insurance may not cover all damages from such claims.
- If third parties on which we depend to conduct our clinical trials do not perform as contractually required, fail to satisfy regulatory or legal requirements or miss expected deadlines, our development program could be delayed with materially adverse effects on our business, financial condition, results of operations and prospects.
- We are dependent on the services of our management and other clinical and scientific personnel, and if we are not able to retain these individuals or recruit additional management or clinical and scientific personnel, our business will suffer.
- We are heavily dependent on third-party service providers to perform critical activities related to the research, development and manufacturing of our product candidates. If these third-party service providers fail to perform, our development program could be delayed with materially adverse effects on our business, financial condition, results of operations and prospects.
- If we are unable to obtain and maintain patent or trade secret protection for any products or product candidates we develop and for our technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize any product candidates or technology we may develop may be adversely affected.
- If we fail to make required payments to AnalytiCon Discovery GmbH, or AnalytiCon, under the terms of the agreement pursuant to which we acquired certain of our core intellectual property, AnalytiCon may exercise remedies that would materially and adversely affect our business and results of operations.
- The market price of our ordinary shares is likely to be highly volatile.
- We do not currently intend to pay dividends on our securities and, consequently, your ability to achieve a return on your investment will depend on appreciation in the price of our ordinary shares.
- We may be a passive foreign investment company, or a PFIC, which could result in adverse U.S. federal income tax consequences to U.S. investors.

3.2 Risk factors

Risks Related to Our Financial Position

We have a limited operating history, have generated no revenues to date and have incurred significant losses since our inception. We expect to incur losses over the next several years, will not generate revenues until we are able to commercialize our products and may never achieve profitability, while our net losses are expected to fluctuate significantly.

We are a clinical-stage biopharmaceutical company with a limited operating history upon which you can evaluate our business and prospects. Since inception, we have incurred significant operating losses and have generated no revenues as we focused on our discovery efforts and developing our product candidates. We expect that it will be several years, if ever, before we have a product candidate ready for commercialization. To date, we have financed our operations primarily through sales of equity. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue clinical development of our current product candidates;
- seek to identify additional product candidates and initiate clinical trials for such additional product candidates;
- acquire or in-license other products and technologies or enter into collaboration arrangements with regards to product discovery;
- seek marketing approvals for our product candidates that successfully complete clinical trials;
- establish a sales, commercialization and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- hire additional personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and
- continue to incur increased costs as a result of operating as a public company.

To become and remain profitable, we must develop and eventually commercialize a product or products with significant market potential. This will require us to be successful in a range of challenging activities, including completing clinical trials of our product candidates, obtaining marketing approval for these product candidates and manufacturing, commercializing and selling those products for which we may obtain marketing approval. We may never succeed in these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our business and could impair our ability to raise capital, maintain our discovery and preclinical development efforts, expand our business or continue our operations and may require us to raise additional capital that may dilute the ownership interest of shareholders. A decline in the value of our business could also cause shareholders to lose all or part of their investment.

We will need substantial additional funding to continue our operations. If we are unable to raise capital when needed or on acceptable terms, we may need to delay, reduce or terminate our product development programs and may be unable to continue as a going concern and could ultimately go into insolvency.

We expect our expenses to increase in parallel with our ongoing activities, particularly as we continue our discovery and preclinical development collaborations to identify new clinical candidates and initiate clinical trials of, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Because the outcome of any clinical trial or preclinical study is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our product candidates. If we do not have sufficient cash and cash equivalents to fund the completion of the research and clinical development of our programs, we will be required to seek a significant amount of additional funds by raising additional equity, convertible financing or non-dilutive financing such as debt financing arrangements, strategic transactions or other means. We may also delay, reduce the scope of, eliminate or divest clinical programs, partner with others or divest one or more of our activities and consider other cost reduction initiatives, such as withholding initiation or expansion of clinical trials or research and slowing down patient recruitment of clinical trials. We may also be required to sell or license to others technologies or clinical product candidates or programs that we would prefer to develop and commercialize ourselves. In the event we are not able to generate sufficient funds from these measures, we may be unable to continue as a going concern, our business, financial condition and/or results of operations could be materially and adversely affected and we may ultimately go into insolvency.

In addition, even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations. Our future funding requirements will depend on many factors, including:

- the progress and cost of our discovery and preclinical development;
- the progress and cost of our clinical trials, including payments of patient cost, clinical investigator cost and payments to CROs that are assisting with our sponsored clinical trials, and other research and development activities;
- the cost and timing of obtaining regulatory approval to commence further clinical trials;
- the costs associated with any future investigator-sponsored clinical trials;
- the cost of filing, prosecuting, defending and enforcing any patent applications, claims, patents and other intellectual property rights;
- the cost and timing of obtaining sufficient quantities of our product candidates for clinical trials by establishing our contracted and/or own production capacities;
- the costs and capital expenditures associated with process optimizations and preclinical and clinical manufacturing;
- the terms and timing of any collaborative, licensing and other arrangements that we may establish;
- the cost of acquiring or licensing additional products or technologies, if any;
- the cost of preparing for launch and commercialization of our product candidates; and
- the cost of operating as a public company in the United States.

There can be no assurance that funding will be available in a timely manner, on favorable terms, or at all, or that such funds, if raised, would be sufficient to enable us to continue to implement our long-term business strategy. Also, general conditions in the global economy, including market volatility resulting from the COVID-19 pandemic or other factors, could adversely impact our ability to access capital as and when needed. If we are unable to obtain sufficient funding in a timely manner or on commercially acceptable terms, we may have to delay, reduce the scope of, eliminate or divest clinical programs, partner with others or divest one or more of our activities, and consider other cost reduction initiatives, such as downsizing our operations, withholding initiation or expansion of clinical trials or research, and slowing down patient recruitment of clinical trials. In the event we are not able to generate sufficient funds, we may be unable to continue as a going concern and our business, financial condition and/or results of operations could be materially and adversely affected and could reduce the price of our ordinary shares and we may ultimately go into insolvency. In addition, any perceived or actual inability by us to finance our clinical development program and other business activities, including as a result of required milestone and royalty payments to third parties, may cause the market price of our ordinary shares to decline.

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

We may seek additional funding through a combination of equity offerings, debt financings, collaborations and/or licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a holder of our ordinary shares. The incurrence of indebtedness and/or the issuance of certain equity securities could result in increased fixed payment obligations and could also result in certain additional restrictive covenants, such as limitations on our ability to incur additional debt and/or issue additional equity, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. In addition, issuance of additional equity securities, or the possibility of such issuance, may cause the market price of our ordinary shares to decline. In the event that we enter into collaborations and/or licensing arrangements in order to raise capital, we may be required to accept unfavorable terms, including relinquishing or licensing to a third-party on unfavorable terms our rights to technologies or product candidates that we otherwise would seek to develop or commercialize ourselves or potentially reserve for future potential arrangements when we might be able to achieve more favorable terms. Additional funding may not be available to us on acceptable terms, or at all. If we are unable to obtain funding on a timely basis, we may be required to significantly curtail one or more of programs or cease operations altogether.

Exchange rate fluctuations could negatively affect our financial condition.

Our consolidated financial statements are presented in euros. We mainly operate via our Dutch and Swiss entities, but we also conduct business in North America and the United Kingdom. Therefore, we have expenses denominated in U.S. dollars and British pound sterling in connection with, among other things, our sponsored clinical trials, purchase of drug product for our clinical trials, process development and the prosecution and maintenance of our intellectual property portfolio. As a result, our business and share price may be affected by fluctuations between the euro and the U.S. dollar and the euro and the British pound sterling, which may have a significant impact on our reported results of operations and cash flows from period to period.

We have identified material weaknesses in our internal control over financial reporting. If we are unable to successfully remediate these material weaknesses and to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud, and as a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our ordinary shares.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. Section 404 of the Sarbanes-Oxley Act requires management of public companies to develop and implement internal control over financial reporting to evaluate the effectiveness thereof. A material weakness is a deficiency or a combination of deficiencies in internal control over financial reporting such that there is a reasonable possibility that a material misstatement of our financial statements will not be prevented or detected on a timely basis. In connection with the preparation of our consolidated financial statements for the fiscal year ended December 31, 2020, we concluded that there were material weaknesses in the design of our internal control over financial reporting across the principles for each component of the COSO framework at the entity level (i.e. control environment, risk assessment, monitoring, information & communication and control activities) and accordingly, across our business and IT processes. The material weaknesses that we identified related to:

- The lack of consistent and documented risk assessment procedures and control activities related to our financial reporting, among which a sufficient level of (management) review and approval, manual processes, roles and responsibilities, and adequate application and controls over information technology; and
- The lack of maintaining a sufficient complement of personnel commensurate with our accounting and reporting requirements, and able to: (i) design and maintain formal accounting policies, procedures and controls over the fair presentation of our financial statements; (ii) analyze, record and disclose complex accounting matters timely and accurately, including share-based compensation arrangements and other non-routine transactions; and (iii) design and maintain controls over the preparation and review of journal entries and financial statements, including maintaining appropriate segregation of duties.

Although several oversight and control activities are performed, not all activities are formalized and documented properly. In addition, where control activities are dependent on information used in a control, we do not perform or document controls to determine the completeness and accuracy of such information. We also did not have controls in place to monitor control activities and identify control deficiencies. Currently, we have only five designated finance employees. To address these material weaknesses, we will need to add personnel and continue to develop and implement new financial processes. We intend to take steps to remediate the material weaknesses described above through hiring additional qualified accounting and financial reporting personnel, and further evolving our accounting processes and policies. We will not be able to fully remediate these material weaknesses until these steps have been completed and have been operating effectively for a sufficient period of time. We cannot assure you that we will be able to successfully remediate the material weaknesses or that other material weakness will not be discovered in the future. If we do not remediate these issues or if we fail to design

and operate effective internal controls in the future, it could result in material misstatements in our financial statements and potentially require us to restate our financial statements which may result in the trading value of our ordinary shares being materially and adversely affected.

Our management will be required to assess the effectiveness of our internal controls over financial reporting on an annual basis pursuant to SOX 404(a), beginning with our Form 20-F for the year ended December 31, 2021. However, for as long as we are an "emerging growth company" under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control over financial reporting pursuant to Section 404(b). We could be an "emerging growth company" for up to five years following this offering. The rules governing the standards that must be met for management to assess our internal control over financial reporting are complex and require significant documentation, testing and possible remediation. Our management may not be able to effectively and timely implement controls and procedures that adequately respond to the increased regulatory compliance and reporting requirements that are applicable to us as a U.S. public company and an assessment of the effectiveness of our internal control over financial reporting by an independent registered public accounting firm in accordance with the provisions of Section 404 could detect additional significant deficiencies or material weaknesses that our management's assessment might not. Undetected material weaknesses in our internal controls could lead to financial statement restatements, require us to incur the expense of remediation and investors may lose confidence in the accuracy and completeness of our financial reports which could cause the market price of our ordinary shares to decline and also restrict our future access to the capital markets. We could be also subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities.

Our tax liability may be materially different from what is reflected in our income tax provisions and related balance sheet accounts.

We are subject to taxation in the Netherlands, Switzerland, the United States and other jurisdictions. Our future effective income tax rate will be impacted by a number of factors, including the geographic composition of our worldwide taxable income and our ability to allocate debt and expenses effectively. If legislators, tax authorities or government agencies in the jurisdictions in which we operate were to change applicable tax laws and regulations (for example, as a result of the various global, regional and local initiatives to reform the international tax framework, such as the base erosion and profit shifting project undertaken by the Organization for Economic Co-operation and Development and anti-tax avoidance measures proposed by the European Committee) or successfully challenge the manner in which our income taxes are currently recognized or calculated or the transfer pricing policies employed by us (including policies set forth in any advance pricing agreements entered into with any taxing authorities), our income tax benefit could decrease, which would adversely impact our cash flow and profitability. Furthermore, in many of these jurisdictions, the tax laws and regulations are very complex and are open to different interpretations and application. The final determination of tax by means of an assessment or an audit could be materially different from our tax provisions and accruals and may negatively impact our financial results.

Our ability to use our net operating losses to offset future taxable income may be subject to certain limitations.

Our ability to use our net operating losses, or NOLs, in the Netherlands and Switzerland is currently limited and may be further limited. In particular, the use of NOLs is subject to limitation in Switzerland, and may expire if unused after a seven-year period. Furthermore, under current Dutch

corporate income tax rules, tax losses can be carried back one year and carried forward six years (and with respect to tax losses incurred up to and including 2018, the carry forward period is nine years). As of January 1, 2022 an indefinite loss-carry forward will apply in the Netherlands (the law proposal has still formally to be enacted). However, both the carry forward (indefinite) and carry back (one year) tax loss relief will be limited to 50% of the taxable profit to the extent it exceeds EUR 1 million, calculated per financial year. As a result of transitional law, tax losses incurred in the financial years that started on or after January 1, 2013 also fall under the new scheme that comes into effect on January 1, 2022 and will therefore be indefinite, but subject to the new limitations as of January 1, 2022.

Risks Related to the Development and Clinical Testing of Our Product Candidates

We are heavily dependent on the success of our product candidates PHVS416 and PHVS719, which are in early stage development and have not yet been assessed for efficacy in a clinical trial. We cannot give any assurance that either product candidate, or any other compounds in development, will successfully complete clinical trials, receive regulatory approval, be commercialized or be differentiated in the market.

We do not have any drugs that have received regulatory approval and may never be able to develop marketable products. We expect that a substantial portion of our efforts and expenses for the foreseeable future will be devoted to the clinical development of our product candidates, PHVS416 and PHVS719, and as a result, our business currently depends heavily on the successful development, regulatory approval and commercialization of these product candidates. We have not yet tested our product candidates in patients with HAE, and to-date we only have data from pre-clinical studies and Phase 1 clinical trials in healthy volunteers. We have not conducted a head-to-head comparison of icatibant or any other drug candidate to PHA121 in a clinical trial. We have compared the published data for icatibant to data from our Phase 1 clinical trial of PHA121. Accordingly, the value of comparisons to icatibant in this report may be limited because they are not derived from a head-to-head trial and they are from trials that were conducted under different protocols at different sites and at different times. Without head-to-head data, we will be unable to make comparative claims for our product candidates, if approved. Future clinical trials may not confirm our analyses to-date. The development of PHVS416 and PHVS719 has been and will continue to be a time-consuming and costly process, and may leave us with insufficient resources to advance other programs and product candidates. We cannot be certain that any PHA121-containing product candidate, including PHVS416 and PHVS719, will receive regulatory approval or be successfully commercialized, even if we receive regulatory approval. The research, testing, manufacturing, safety, efficacy, labeling, approval, sale, advertising promotion, commercialization and distribution of our product candidates are, and will remain, subject to comprehensive regulation by the FDA in the United States, the European Union and the EMA in Europe and regulatory authorities in other countries, with regulations differing from country to country. We will not be permitted to market our drug candidates in the United States or Europe until we receive approval of a New Drug Application, or NDA, from the FDA or a marketing authorization, or MA, from the European Commission (based on the positive opinion of the EMA), respectively. We have not submitted any marketing authorization applications for any of our product candidates. NDAs and MAs must include extensive preclinical and clinical data and supporting information to establish the drug candidate's safety and effectiveness for each desired indication. The preclinical and clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of drug development, including failure to demonstrate efficacy or safety, the occurrence of adverse events that

are severe or medically or commercially unacceptable, our or our partners' failure to comply with trial protocols, applicable regulatory requirements, and industry standards, or a determination by the FDA or any comparable foreign regulatory authority that a product candidate may not continue development or be approved in accordance with our development plans or at all. We cannot guarantee that any preclinical studies and clinical trials will be conducted as planned or completed on schedule, if at all, or that the results of such trials will be sufficient to support regulatory approval for our product candidates. Failure to obtain regulatory approval for any of our product candidates PHVS416 and PHVS719 or any other product candidate in the United States, Europe or other jurisdictions will prevent us from commercializing and marketing these products in such jurisdictions.

Even if we were to successfully obtain approval from the FDA, EMA and comparable foreign regulatory authorities for our product candidates, any approval might contain significant limitations related to use restrictions for specified age groups, warnings, precautions or contraindications, or may be subject to burdensome post-approval study or risk management requirements. We may also be limited in our ability to advertise, promote and/or market our product candidates in a way that successfully differentiates them in the market. For example, we may not be able to position our product as safer, more effective, more convenient, or better for a patient's quality of life. Furthermore, we will still need to develop a commercial infrastructure, or otherwise develop relationships with collaborators to commercialize, establish a viable pricing structure and obtain coverage and adequate reimbursement from third-party payors, including government healthcare programs. If we, or our collaborators, are unable to successfully commercialize any product candidate, we may not be able to generate sufficient revenue to continue our business.

Our business and operations may be adversely affected by a variety of events outside our control, including pandemics, epidemics or outbreaks of infectious diseases, such as the recent COVID-19 pandemic.

A wide variety of events beyond our control, including natural or man-made disasters, power shortages, fires, extreme weather conditions, pandemics, epidemics or outbreaks of infectious diseases, political unrest or other events could disrupt our business or operations or those of our development partners, manufacturers, regulators or other third parties with whom we conduct business now or in the future. These events may cause businesses and government agencies to be shut down, supply chains to be interrupted, slowed, or rendered inoperable, and individuals to become ill, quarantined, or otherwise unable to work and/or travel due to health reasons or governmental restrictions. For instance, the spread of COVID-19 has impacted the global economy and impacted our operations, including through interruptions of our, or delays to, clinical trial activities, regulatory reviews, manufacturing activities and supply chain. The COVID-19 outbreak has delayed, and may continue to delay, enrollment in our clinical trials due to prioritization of hospital resources toward the outbreak or other factors, and some patients may be unwilling to enroll in our trials or be unable to comply with clinical trial protocols if quarantines impede patient movement or interrupt healthcare services, which would delay our ability to conduct clinical trials or release clinical trial results and could delay our ability to obtain regulatory approvals and commercialize our product candidates. For example, we experienced an approximate two-month delay in starting the enrollment of our now completed Phase 1 multiple ascending dose study of PHA121 in healthy volunteers as a result of COVID-19. In addition, even with our distributed operations and our observation of social distancing measures, there remains the possibility that key personnel may become ill or are otherwise unable to work, which could affect our operations.

Furthermore, the spread of the virus may affect the operations of key governmental agencies,

such as the FDA, which may delay the development of our product candidates. The spread of an infectious disease, including COVID-19, may also result in the inability of our suppliers to deliver components or raw materials, and the inability of our CDMOs to provide supplies of our product candidates for our planned clinical trials, on a timely basis or at all. Further, it may impact the ability of our CROs, including non-clinical CROs, to provide services to support our clinical program. In addition, hospitals may reduce staffing and reduce or postpone certain treatments in response to the spread of an infectious disease. Such events may result in a period of business disruption, and in reduced operations, or doctors and medical providers may be unwilling to participate in our clinical trials, any of which could materially affect our business, financial condition and results of operations. The extent to which the COVID-19 pandemic impacts our business will depend on future developments, which are uncertain and cannot be predicted, including new information which may emerge concerning the severity of the COVID-19 pandemic and the actions to contain COVID-19 or treat its impact, among others. If we are unable to meet our milestones it might jeopardize our funding opportunities.

In addition, the COVID-19 pandemic has already caused, and is likely to result in further, significant disruptions and uncertainties in global financial markets, which may reduce our ability to access capital on favorable terms or at all. A recession, depression or other sustained adverse market event resulting from the spread of COVID-19 could also materially and adversely affect our business and the value of our ordinary shares. The ultimate impact of the COVID-19 pandemic or a similar health epidemic is uncertain and subject to change. To the extent the COVID-19 pandemic adversely affects our business and financial results, it may also have the effect of heightening many of the other risks described in this "Risk Factors" section, such as those relating to our clinical and preclinical development operations, manufacturing activities, the supply chain for our ongoing and planned clinical trials and our ability and need to raise additional capital to support our operations.

Disruptions at FDA, EMA and other government agencies caused by funding shortages or global health concerns such as COVID-19 could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, cleared or approved or commercialized in a timely manner or at all, which could negatively impact our business.

The ability of the FDA, EMA and other comparable government agencies to review and clear or approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory, and policy changes, ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect their ability to perform routine functions. Government funding of government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA, EMA and other agencies may also slow the time necessary for new drugs or modifications to cleared or approved drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For instance, in response to COVID-19, on March 10, 2020, the FDA announced its intention to postpone most foreign inspections of manufacturing facilities and products. Foreign pre-approval and for-cause inspection assignments that are not deemed mission-critical remain temporarily postponed, while those deemed "mission-critical" are being considered for inspection on a case-by-case basis. Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the COVID-19 pandemic. In addition, regulatory agencies have generally reduced face-to-face interactions relative to the pre-pandemic situation which may impact our ability to reach consensus with regulators. If a prolonged government shutdown occurs,

or if global health concerns continue to prevent the FDA, EMA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA, EMA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

We may not be able to design and develop an extended-release formulation.

Our current strategy includes developing an extended-release formulation for the PHA121 prophylactic indication. We have not yet identified a specific extended-release formulation. If we pursue this development strategy, we expect to file for and obtain patents covering the specific formulation developed, as well as its use for the treatment of HAE. There can, however, be no assurance that such an extended-release formulation will be successfully developed in a timely manner, that adequate patent protection can be obtained or that any such formulation would provide us with a commercial advantage. If we are unable to develop this extended-release formulation on our own, we may need to in-license patented technology to do so. Many third parties have patents covering technologies and manufacturing processes needed to develop and make extended-release formulations and there can be no assurance that we would be able to obtain rights to such patents on attractive financial terms, if at all.

We may experience setbacks in our clinical trials, including delays in commencing, conducting or completing our clinical trials. Moreover, we have established proof-of-mechanism for PHA121 and have designed and advanced our future clinical development program based on a clinical trial that assessed a surrogate endpoint, as well as modelling of our results from that trial with additional in vitro and in vivo data and comparisons to published results for other currently available products from different trials. We may not be able to replicate these results or analyses in future clinical trials that assess the endpoints required to obtain regulatory approval or we may have inconclusive or negative results. Any setbacks in our clinical development program could have a material adverse effect on our business, financial condition, results of operations and prospects.

Clinical trials are expensive and complex. Each trial can take many years to complete and have uncertain outcomes. Failure of a product can occur at any stage of the testing, including later phases of clinical trials despite having progressed through preclinical and early phase clinical trials, for a variety of reasons, such as changes in formulation of the product, differences in patient populations, changes in trial and manufacturing protocols and complexities of larger, multi-center trials, among others. The results from preclinical or early phase clinical trials of a product candidate may not predict the results that will be obtained in later phase clinical trials of the product candidate. For example, we have established proof-of-mechanism for PHA121 and have designed and advanced our future clinical development program based on a clinical trial that assessed a surrogate assessment, as well as modelling of our results from that trial with additional in vitro and in vivo data and comparisons to published results for other currently available products from different trials. We may not be able to replicate these results or analyses in future clinical trials that assess the endpoints required to obtain regulatory approval. We, the FDA or other applicable regulatory authorities may suspend or terminate clinical trials of a product candidate at any time for numerous reasons, including, but not limited to, a belief that subjects participating in such trials are being exposed to unacceptable health risks or adverse side effects, or other adverse experiences or findings. Even if clinical trials are successful, before granting approval to any product candidate, regulatory authorities can request additional clinical trials, including with larger patient numbers, find deficiencies in the manufacturing processes or facilities upon which we rely and change their approval policies or regulations or their prior guidance to us during clinical development

in a manner that renders our clinical data insufficient for approval.

We have, and may continue to experience numerous setbacks during, or as a result of, the clinical trial process that experienced could delay or prevent the commencement, conduct and completion of clinical trials or the commercialization of our current and any future programs, such as:

- delays in reaching a consensus with regulatory agencies on the design or implementation of our clinical trials, including with respect to our strategy for sharing Phase 1 data between PHVS416 and PHVS719 programs and designs for improving the efficiency of our clinical development path;
- delays in obtaining regulatory approval or ethics committee approval to commence a clinical trial;
- delays in reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- failure of CROs to adequately supervise investigators;
- failure to recruit sufficient investigators or recruit and enroll sufficient subjects for our clinical trials in a timely manner or at all, including due to the COVID-19 pandemic;
- delay or failure in having subjects complete a trial or return for post-treatment follow-up, including due to the COVID-19 pandemic;
- failure to obtain and maintain the required institutional review board, or IRB, or ethics committee approval at each clinical trial site;
- clinical sites or investigators deviating from trial protocol or dropping out of a trial;
- lack of adequate funding to continue a clinical trial;
- delays in sufficiently developing, characterizing or controlling a manufacturing process suitable for advanced clinical trials;
- clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon product development programs; or
- failure of ourselves or any third-party manufacturers, contractors or suppliers to comply with regulatory requirements, maintain adequate quality controls, or be able to provide sufficient product supply to conduct and complete clinical trials of our product candidates.

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

If we suffer any material delays, negative results or other setbacks in our clinical trials or if our clinical trials are put on clinical hold or terminated, we may incur increased costs or be unable to continue development of PHA121, including our product candidates PHVS416 and PHVS719, which

could have a material adverse effect on our business, financial condition, results of operations and prospects.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented and expenses for development of our product candidates could increase.

We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials to demonstrate safety and efficacy. We are currently conducting early phase clinical trials and have commenced a Phase 2 trial in the on-demand setting which we expect will provide critical data for dose selection for the prophylaxis indication. We do not know whether planned or ongoing clinical trials will enroll subjects in a timely fashion, require redesign of essential trial elements or be completed on our projected schedule. In particular, because we are focused on patients with HAE, which is a rare disease, our ability to enroll eligible patients in trials may be limited or may result in slower enrollment than we anticipate. In addition, competitors have ongoing clinical trials for product candidates being studied for the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Patient enrollment can also be affected by a number of other factors including:

- the eligibility criteria for the study in question;
- the perceived risks and benefits of the product candidate under study;
- the efforts to facilitate timely enrollment in clinical trials;
- the availability of existing or experimental treatments affecting our ability to recruit patients;
- the inability to identify and maintain a sufficient number of trial sites, many of which may already be engaged in other clinical trial programs, including some that may be for the same disease indication;
- the patient referral practices of physicians;
- the proximity and availability of clinical trial sites for prospective patients;
- any delays and difficulties in enrollment due to the COVID-19 pandemic;
- ambiguous or negative interim results of our clinical trials, or results that are inconsistent with earlier results;
- feedback from the FDA, EMA and any comparable foreign regulatory authority, data safety monitoring boards, or a comparable foreign regulatory authority, or results from earlier stage or concurrent preclinical studies and clinical trials, that might require modifications to the protocol;
- decisions by the FDA, EMA and any comparable foreign regulatory authority or us, or recommendations by data safety monitoring boards, to suspend or terminate clinical trials at any time for safety issues or for any other reason; and
- unacceptable risk-benefit profile, perceived or actual, or unforeseen safety issues or adverse effects.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays, may result in increased development costs for our product candidates, and could also require us to abandon one or more clinical trials altogether, any of which could cause a material adverse effect on our business, financial position and results of operations.

Clinical trials of our product candidates may not uncover all possible adverse effects that patients may experience.

Clinical trials are conducted in a limited sample of the patient population for the disease or condition under study; the actual patient population may have significantly more variability than the clinical trial subjects. In addition, clinical trials are, by design, limited with respect to the number of subjects and the duration of exposure to the product candidate. As a result of such limitations, we cannot be sure that all side effects of our product candidates may be uncovered during our clinical trials or that a complete safety profile of our product candidates will be identified. Further, even larger clinical trials may not identify rare serious adverse effects or the duration of such studies may not be of sufficient length to identify when those events may occur. There have been other products that have been approved by the regulatory authorities but for which safety concerns have been uncovered following approval. Such safety concerns have led to labeling changes, the imposition of other regulatory requirements (e.g., Risk Evaluation and Mitigation Strategy or REMs, or post-authorization safety studies, or PASS) or withdrawal of products from the market, and any of our product candidates may be subject to similar risks.

Although to date we have not seen evidence of significant safety concerns with our product candidates currently in clinical trials, patients treated with our products, if approved, may experience adverse reactions and it is possible that the FDA or other regulatory authorities may ask for additional safety data as a condition of, or in connection with, our efforts to obtain approval of our product candidates. If safety problems occur or are identified after our product candidates reach the market, we may, or regulatory authorities may require us to amend the labeling of our products, institute a REMs or PASS, recall our products or even withdraw approval for our products.

Clinical development is a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials as well as data from any interim analysis of ongoing clinical trials may not be predictive of future trial results. Clinical failure can occur at any stage of clinical development.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. Although product candidates may demonstrate promising results in early clinical (human) trials and preclinical (animal) studies, they may not prove to be safe or effective in subsequent clinical trials. For example, the results of animal studies may not accurately predict human experience. Likewise, early clinical trials may not be predictive of eventual safety or effectiveness results in larger-scale pivotal clinical trials. In this report we discuss the potency of PHA121 as shown in preclinical and Phase 1 clinical trials. Potency as used in this report refers to the amount of drug required to produce a pharmacological effect of given intensity and is not a measure of therapeutic efficacy. We do not yet have data from any PHA121 Phase 2 clinical trial to evaluate the potential therapeutic efficacy of PHA121 in HAE patients. The results of preclinical studies and early clinical trials, as well as data from interim analysis of ongoing clinical trials, may not be predictive of the results of ongoing or future clinical trials. In addition, the studies and trials of other products with similar mechanisms of action to our product candidates may not be predictive of our clinical trial results. There can be significant variability in safety and/or efficacy results between different trials of the same product candidate due to numerous factors, including changes in trial protocols, differences in composition of the patient populations, adherence to the dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. Product candidates in later phase clinical trials may fail to show the desired safety and efficacy traits despite having progressed

through preclinical studies and earlier clinical trials. In addition to the safety and efficacy trials of any product candidate, clinical trial failures may result from a multitude of factors including flaws in trial design, dose selection, placebo effect and patient enrollment criteria. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials, and it is possible that our product candidates will as well which may have an adverse effect on our business and the value of the ordinary shares.

We may not be able to conduct, or contract others to conduct, animal testing in the future, which could harm our research and development activities.

Certain laws and regulations relating to drug development require us to test our product candidates on animals before initiating clinical trials involving humans. Animal testing activities have been the subject of controversy and adverse publicity. Animal rights groups and other organizations and individuals have attempted to stop animal testing activities by pressing for legislation and regulation in these areas and by disrupting these activities through protests and other means. To the extent the activities of these groups are successful, our research and development activities may be interrupted or delayed.

Risks Related to Regulatory Approval of Our Clinical Development Programs and Our Product Candidates

Clinical development is subject to extensive regulation, which can be costly and time-consuming to comply with, and we may not obtain approvals for performing clinical trials or for marketing any of our product candidates.

We are not permitted to conduct clinical trials with or market any product candidate until we obtain authorization from the appropriate regulatory authorities. We must obtain authorization for conducting clinical trials with any product candidate and for marketing any product candidate from the appropriate regulatory authority of each jurisdiction in which we wish to perform clinical trials with or market our product candidates.

Since the 1990s, many companies have tried but failed to discover oral B2 antagonists, as the bradykinin- B2-receptor proved to be a difficult target for the development of orally available antagonists. Current treatment guidelines also recommend against the use of the traditionally used oral HAE medications, such as antifibrinolytics (tranexamic acid or epsilon aminocaproic acid), due to limited efficacy. As our product candidates are based on novel technologies, it is difficult to predict the time or costs associated with the regulatory approval process or be certain of our ability to successfully commence, conduct, and complete clinical development, or obtain the necessary regulatory and reimbursement approvals required for the commercialization of our product candidates PHVS416 and PHVS719. As discussed under "—Risks Related to the Development and Clinical Testing of Our Product Candidates—We may experience setbacks in our clinical trials, including delays in commencing, conducting or completing our clinical trials, as well as inconclusive or negative results, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects," we or our partners may experience any number of unfavorable outcomes during or as a result of preclinical studies and clinical trials which could delay or prevent regulatory approval of our product candidates, or negatively impact our management's credibility, our value and our operating results.

We may invest substantial time and resources in preclinical studies, clinical trials,

manufacturing and the preparation and submission of various regulatory applications without any assurance that we will obtain regulatory approval or recoup our investment. The FDA and other regulatory authorities exercise substantial discretion with respect to the development and approval of drug product candidates. The number, size and design of preclinical studies and clinical trials that will be required for regulatory approval will vary depending on the program, the primary indication and the specific regulations and guidance documents applicable to any particular program. The FDA and other regulatory authorities can delay, limit or deny (i) clinical trial development (e.g., placing a clinical trial under clinical hold) and (ii) approval of a program for many reasons, including:

- manufacturing related issues or concerns;
- concerns relating to the product candidate's safety or efficacy;
- concerns relating to the design, control or conduct of preclinical studies and clinical trials including the use of placebo or active controls in blinded studies;
- negative or ambiguous results of any preclinical or clinical trial;
- concerns relating to the sufficiency of clinical trial results;
- the failure of more advanced clinical results to confirm positive results from preclinical studies or earlier clinical trials; or
- the development or observation of unexpected safety issues, adverse events or adverse side effects.

Should any of these or other factors affecting our development programs or product candidates occur, regulatory approval of our product candidates could be denied, delayed or have conditions placed upon it. Failure to obtain regulatory approval in a timely manner, in a limited manner or at all would have a material adverse effect on our business, financial condition, results of operations or prospects.

Additionally, effective as of January 31, 2020, the United Kingdom withdrew from the European Union, a process referred to as "Brexit". Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, the final resolution of the withdrawal of the United Kingdom from the European Union could materially impact the regulatory regime with respect to the approval of any of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for any of our product candidates, which could significantly and materially harm our business.

There can be no assurance that we will be able to obtain or, if obtained, maintain orphan drug status.

We currently do not have orphan drug designations in respect of our PHVS416 and PHVS719 product candidates. There is no assurance that we will be able to obtain orphan drug designations for our product candidates in indications that are important to our business or if obtained, to gain orphan drug exclusivity for our product candidates in indications that are important for our business. Orphan drug exclusivity confers market exclusivity, subject to certain limitations, upon the first product to receive marketing approval by the relevant regulatory authority for the jurisdiction and entails the right to market exclusively the product for the specified indication, during a maximum of ten years for the

European Union and during a period of seven years in the United States. The period of exclusivity in the European Union may be reduced to six years if, at the end of the fifth year, the product no longer meets the criteria for orphan drug designation if, among other things, it is established that the product is sufficiently profitable not to justify market exclusivity.

Even if we obtain orphan drug exclusivity for a product in the U.S., an approval may be granted to other applicants of a similar product for the same indication if we are unable to supply sufficient quantities of the product, we consent to such an approval, or if the product of a second applicant is deemed to be clinically superior to our product. Changes to the current regulatory frameworks governing orphan drugs may also impact existing and future market exclusivities provided as a result of orphan drug designation. Even if we were to succeed in obtaining and maintaining market exclusivity for any future products through orphan drug status, the orphan drug regulations would not preclude competitors from developing or marketing different products for the same indications to which our programs are directed, or from independently developing versions of our products for different indications. Further, we may lose orphan drug exclusivity if the EMA or the FDA determines that the request for designation was materially defective. If we fail to obtain or maintain orphan exclusivity for any future products, or if the commercial value of market exclusivity is diminished, our competitive position or financial and commercial prospects could be materially adversely affected.

If we fail to comply with ongoing regulatory obligations and restrictions following regulatory approval of any product candidate, regulatory authorities may take enforcement action against us, for example, any regulatory approval granted could be withdrawn or revoked and sale of any products could be suspended or financial penalties could be imposed.

If any of our product candidates are approved for commercialization by the FDA or another regulatory authority, we would be subject to extensive regulatory requirements over, among other things, product manufacturing, testing, labeling, packaging, storage, advertising, promotion, marketing, distribution, export, import, adverse event reporting and record keeping. These requirements include submissions of safety and other post-commercialization information and reports, drug establishment registration and drug listing requirements, current Good Manufacturing Practices, or cGMP, relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents. In addition, we would be subject to other requirements regarding the distribution of drug samples to physicians. We and our suppliers, CDMOs and contract testing laboratories would also be subject to inspection by the FDA or other regulatory authorities to determine compliance with these requirements. In addition, facilities in the European Union that manufacture any of our product candidates must be licensed by the relevant regulatory authorities. In the United States, there are also certain state requirements with respect to drug manufacturing and distribution with which we must comply.

The FDA, or other regulatory authorities, may also impose significant limitations on the uses or marketing of our approved product candidates, which could reduce the potential market for any products. The FDA and other regulatory authorities closely regulate the post-approval advertising, promotion, and commercialization of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding use of their products and if we promote our products beyond their approved indications or in other ways that violate FDA requirements, we may be subject to enforcement action for, among other things, off-label promotion. In the EU, promotion of prescription-only drugs to the general public as well as off-label promotion are strictly prohibited and can result in

significant fines and reputational damage. For the United States, alleged, or potential violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws. Advertising, promotion, and marketing activities may also give rise to litigation by competitors.

The FDA, or other regulatory authorities, may also impose requirements for costly post-commercialization studies or clinical trials and surveillance to monitor the safety or efficacy of an approved drug. Previously unknown problems with the drug may result in restrictions on the commercialization of the product and could include withdrawal of the drug from the market.

In addition, as discussed under "—Risks Related to the Development and Clinical Testing of Our Product Candidates—We and our partners may be subject to new legislation, regulation, regulatory proposals and healthcare payor initiatives that may increase our costs of compliance and adversely affect our or our partners' ability to market our products, obtain collaborators and raise capital," new statutory requirements or additional regulations or initiatives may be enacted. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations. Failure to comply with the requirements of the FDA and other applicable regulatory authorities may also subject us to administrative or judicially imposed sanctions, including civil and criminal penalties, injunctions, product seizure or recall, import bans, restrictions on the conduct of our operations, total or partial suspension of production and refusal to approve a pending new drug application, or NDA, and financial penalties. If we are subject to any of these sanctions, our competitive position or financial and commercial prospects could be materially adversely affected.

We and our partners may be subject to new legislation, regulation, regulatory proposals and healthcare payor initiatives that may increase our costs of compliance and adversely affect our or our partners' ability to market our products, obtain collaborators and raise capital.

In various jurisdictions including the United States, there have been and continue to be a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, subject us to more stringent drug labeling and post- commercialization testing or restrict or regulate post-approval activities and affect our ability, or the ability of our future collaborators, to profitably sell any product candidates for which we obtain marketing approval.

Among policy makers and payors in various jurisdictions, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. For example, in the United States, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively, the ACA), enacted in 2010, has had a significant impact on the healthcare industry. The ACA increased federal oversight of private health insurance plans and included a number of provisions designed to reduce Medicare expenditures and the cost of health care generally, to reduce fraud and abuse, and to provide access to increased health coverage.

Since its enactment there have been judicial, Presidential and Congressional challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA. While Congress has not enacted legislation to comprehensively repeal the ACA, at least two bills

affecting the implementation of the ACA have been signed into law, including the repeal, effective January 1, 2019, of the tax based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly referred to as the "individual mandate." In December 2018, a federal district court in Texas ruled that the ACA's individual mandate, without the penalty that was repealed effective January 1, 2019, was unconstitutional and could not be severed from the ACA. As a result, the court ruled the remaining provisions of the ACA were also invalid. The Fifth Circuit Court of Appeals affirmed the district court's ruling that the individual mandate was unconstitutional, but it remanded the case back to the district court for further analysis of whether the mandate could be severed from the ACA (i.e., whether the entire ACA was therefore also unconstitutional). The Supreme Court of the United States granted certiorari on March 2, 2020, heard oral arguments on the case on November 10, 2020 and the case is expected to be decided in 2021.

Further, the Trump administration took several executive actions, including the issuance of a number of executive orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. An under-staffed FDA could result in delays in the FDA's responsiveness or in its ability to review submissions or applications within the established Prescription Drug User Fee Act time frames, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all. In the coming years, additional legislative and regulatory changes could be made to governmental health programs that could significantly impact pharmaceutical companies and the success of our product candidates. As such, we cannot predict what effect the ACA or other healthcare reform initiatives that may be adopted in the future will have on our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per financial year effective April 1, 2013 and, due to subsequent legislation, will stay in effect through 2030, unless additional Congressional action is taken, with the exception of a temporary suspension of the payment reduction from May 1, 2020 through December 31, 2020 enacted as part of the CARES Act. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding.

Further, in the United States, there has been heightened governmental scrutiny recently over the manner in which drug manufacturers set prices for their marketed products. For instance, on September 13, 2020, President Trump issued an executive order directing the Secretary of Health and Human Services to pursue implementation of two new payment models under which Medicare would test whether paying no more than the "most-favored- nation" price for certain included drugs and biological products covered under Part B and Part D, respectively, would mitigate poor clinical outcomes and increased Medicare expenditures associated with high drug costs. If implemented, the "most-favored-nation" price would generally reflect the lowest price, after certain adjustments, for a pharmaceutical product sold in an economically-comparable member country of the Organisation for Economic Co-operation and Development. The U.S. Congress has also continued to conduct inquiries into the prescription drug industry's pricing practices. At the state level in the United States, legislatures are also increasingly passing legislation and states are implementing regulations designed to control spending

on, and patient out of pocket costs for, drug products.

In some countries outside the United States, the proposed pricing for a treatment must be approved before it may be lawfully marketed. In addition, in some markets, the pricing of prescription drugs is subject to government control and reimbursement which may in some cases be unavailable. The requirements governing drug pricing vary widely from country to country. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our product candidates that may be approved. Historically, pharmaceutical products launched in the European Union do not follow price structures of the United States and generally tend to have significantly lower prices.

These efforts and other healthcare reform measures that may be adopted in the future may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product, and any reduction in reimbursement from any government program may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenues, attain profitability, or commercialize our product candidates, if approved.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action in the United States, the European Union or another jurisdiction, or the effect that any such future legislation or administrative action may have on our business.

Risks Related to Our Operations

Due to our limited resources and access to capital, we must prioritize development of certain programs and our decision to pursue these programs may prove to be unsuccessful as they may never receive regulatory approval or achieve profitability.

Because we have limited resources and access to capital to fund our operations, we must decide which product candidates to pursue and the amount of resources to allocate to each product candidate. As such, we are currently primarily focused on the development of PHVS416 and PHVS719. These, and future decisions concerning the allocation of capabilities, infrastructure, management and financial resources towards particular programs or therapeutic areas may not lead to the development of viable commercial products and may divert resources from better opportunities. Similarly, these and future decisions to delay or terminate product development programs could cause us to miss valuable opportunities. If we make incorrect determinations regarding the market potential of our product candidates or misread trends in the pharmaceutical industry, our business, financial condition and results of operations could be materially adversely affected.

If we cannot manufacture our product candidates in sufficient amounts, with CDMOs or ourselves, at acceptable costs and on a timely basis, we may be unable to supply sufficient product candidates for preclinical or clinical trials or to support commercialization of our product candidates, if approved.

We do not own or operate manufacturing facilities and have no plans to build our own clinical or commercial-scale manufacturing capabilities. We cannot ensure that our suppliers will remain in business, have sufficient capacity or supply to meet our needs, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to work with us. If we cannot establish sufficient supply through alternative third-party CDMOs or in our own facilities should we

develop these, our ability to conduct the planned and future clinical trials and our plans for commercialization would be materially adversely affected.

In addition, we currently rely on a single CDMO for the production of certain of our product candidates and, as a result, face certain additional risks relating to our manufacturing operations. A single significant disruptive event at the manufacturing operations of our CDMO can have a material adverse effect on our business, prospects, financial condition and results of operations. In addition, our CDMO is located in the United Kingdom and we cannot rule out the possibility of delays in obtaining our product candidates as a result of changes in the governing regulatory framework, including import/export restrictions, due to Brexit. Business interruption insurance may not adequately compensate us for any losses that may occur and we would have to bear the additional cost of any disruption. For instance, if we were to experience an unexpected loss of supply, or if our CDMO was unable to meet our demand for our product candidates or their services, we could experience delays in our research and development activities, planned clinical trials or commercialization of approved products. In the first quarter of 2021, we learned that our CDMO discovered a packaging issue with certain batches of packaging of soft capsules for our RAPIDe-1 trial. The issue was investigated and we commenced the RAPIDe-1 trial for on-demand treatment of HAE attacks in February 2021. Finding alternative CDMOs or suppliers of acceptable quality who can deliver appropriate volumes at acceptable cost may be challenging. Moreover, the long transition periods involved in the change of CDMOs and suppliers, if necessary, would significantly delay our clinical trials and the commercialization of our product candidates, if approved.

We will need to work with CDMOs that can meet all applicable FDA and other regulatory authority requirements on an ongoing basis. If the manufacturing process is changed during the course of product development, the FDA or other regulatory authorities could require us to repeat some or all previously conducted trials or conduct additional trials to obtain bridging data, which could delay or impede our ability to obtain marketing approval. If we or our CDMOs are unable to reliably produce and release our product candidates to specifications acceptable to FDA or other regulatory authorities, we may not obtain or maintain the approvals we need to further develop, conduct clinical trials for, and commercialize such product candidates. Similarly, approval of our product candidates could be delayed or denied if the intended manufacturing site fails to pass the required preapproval inspection. Even if we obtain regulatory approval for any of our product candidates, there is no assurance that either we or our CDMOs will be able to manufacture the approved product to specifications acceptable to the FDA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical trials, require clinical trials to obtain bridging data or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates, impair commercialization efforts, increase our cost of goods, and have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We expect that development of our own manufacturing facilities could provide us with enhanced control of material supply for our product candidates for the clinical trials and the commercial market. However, we have no experience as a company in developing and operating a manufacturing facility and may never be successful in developing our own manufacturing facility or capability should we decide to do so. In particular, if we do pursue the construction of our own manufacturing facilities, we may not complete construction in a timely manner, if at all. Such facilities would also need to be inspected and approved by the FDA and other regulatory agencies before these facilities can be used to manufacture our product candidates, which may subject us to unforeseen delays in our manufacturing

efforts and additional regulatory inspections.

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

Manufacturing issues may arise that could increase product and regulatory approval costs or delay commercialization of our products.

As the manufacturing processes are scaled up they may reveal manufacturing challenges or previously unknown impurities that could require resolution in order to proceed with our planned clinical trials and obtain regulatory approval for the commercial marketing of our products. In the future, we may identify manufacturing issues or impurities that could result in delays in the clinical program and regulatory approval for our products, increases in our operating expenses, or failure to obtain or maintain approval for our products. Our reliance on third-party manufacturers entails risks, including the following:

- the inability to meet our product specifications, including product formulation, and quality requirements consistently;
- a delay or inability to procure or expand sufficient manufacturing capacity;
- manufacturing and product quality issues, including those related to scale-up of manufacturing;
- a failure to comply with cGMP and similar quality standards;
- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- operations of our third-party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier;
- carrier disruptions or increased costs that are beyond our control; and
- the failure to deliver our products under specified storage conditions and in a timely manner.

Any of these events could lead to delays in any clinical trial we may undertake, failure to obtain regulatory approval or impact our ability to successfully commercialize any product candidates. Some of these events could be the basis for FDA or other regulatory authorities' action, including injunction, recall, seizure, or total or partial suspension of production.

Our third-party manufacturers or suppliers may use potent chemical agents and hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time consuming or costly.

Our third-party manufacturers or suppliers may use hazardous materials, including chemicals and biological agents and compounds that could be dangerous to human health and the safety of the environment. The operations of our third-party manufacturers and suppliers also produce hazardous waste products. Various laws and regulations govern the use, generation, manufacture, storage, handling and disposal of these materials and wastes. Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our product development efforts. In addition, we cannot eliminate the risk of accidental injury or contamination from these materials or wastes and we may be sued for any injury or contamination that results from our use or the use by third parties of these materials. In the event of contamination or injury,

we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended.

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

Our activities rely heavily on sensitive and personal materials and information, an area which is highly regulated by privacy laws. Our failure to comply with such laws or to adequately secure the information we hold could result in significant liability or reputational harm and, in turn, a material adverse effect on our client base, member base and revenue. Further, if we are unable to generate or maintain access to essential patient samples or data for our research and development and manufacturing activities for our programs, our business could be materially adversely affected.

As a result of our clinical development, we will have access to very sensitive data regarding the patients enrolled in our clinical trials, and our current and future product candidates will rely on the use of patient and donor data and material. This data will contain information that is personal in nature, and the maintenance of this data is subject to certain privacy-related laws, which impose administrative burdens, substantial costs and litigation risks upon us, such as the rules promulgated by the U.S. Department of Health and Human Services under the U.S. Health Insurance Portability and Accountability Act, or HIPAA, and U.S. state privacy laws. These rules inter alia require that written authorizations from patients are obtained and that policies, procedures and reasonable and appropriate security measures are implemented that protect individually identifiable health and other information we receive and to ensure that such information is used only as authorized by the patient. If the patient fails to execute an authorization or the authorization fails to contain all required provisions, then we will not be allowed access to the patient's information and our research efforts can be substantially delayed. Also, any violations of these rules by us could subject us to civil and criminal penalties and adverse publicity and could harm our ability to initiate and complete clinical trials.

In addition, there are significant international laws that protect data privacy which we must adhere to. For example, we are subject to the EU General Data Protection Regulation, or the GDPR (as implemented by countries in the EEA), which applies extra-territorially and imposes onerous requirements on controllers (e.g., sponsors) and processors (e.g., CROs, laboratories) of personal data, including, for example: (i) accountability and transparency requirements, and enhanced requirements for obtaining valid consent; (ii) obligations to consider data protection as any new products or services are developed and to limit the amount of personal data processed; (iii) obligations to comply with data protection rights of data subjects; and (iv) reporting of personal data breaches to the supervisory authority without undue delay (and no later than 72 hours). The GDPR also prohibits the international transfer of personal data from the EEA to countries outside of the EEA unless made to a country deemed to have adequate data privacy laws by the European Commission or where a data transfer mechanism has been put in place. Until recently, one such data transfer mechanism was the EU-US Privacy Shield. However, in July 2020 the Court of Justice of the European Union, or the CJEU, declared the Privacy Shield to be invalid. The CJEU upheld the validity of the standard contractual clauses, or SCCs, as a legal mechanism to transfer personal data but companies relying on SCCs will—subject to additional guidance from regulators in the EEA– need to evaluate and implement supplementary measures that

provide privacy protections additional to those provided under SCCs. In turn, the findings of the CJEU will have significant implications for cross-border data flows. Further, the GDPR provides that countries in the EEA may establish their own laws and regulations further restricting the processing of certain personal data, including genetic data, biometric data, and health data.

We have relatively limited experience with the relevant privacy and security policies, practices and regulations, and cannot assure that our policies and practices will be sufficient to protect us from liability or adverse publicity relating to the privacy and security of personal data. Privacy laws, rules and regulations also evolve frequently and their scope may continually change, through new legislation, amendments to existing legislation and changes in enforcement, and may be inconsistent from one jurisdiction to another. The interpretation and application of consumer, health-related and data protection laws, especially with respect to genetic samples and data, in the United States, the European Union and elsewhere, are often uncertain, contradictory and in flux. As a result, implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future, and we cannot determine the impact such future laws, regulations and standards may have on our business. We cannot provide assurance that current or future legislation will not prevent us from generating or maintaining personal data or that patients will consent to the use of their personal data (as necessary); either of these circumstances may prevent us from undertaking or publishing essential research and development, manufacturing and commercialization, which could have a material adverse effect on our business, results of operations, financial condition and prospects.

Complying with these various laws and regulations could cause us to incur substantial costs or require us to change our business practices, systems and compliance procedures in a manner adverse to our business. For example, failure to comply with the GDPR requirements could result in regulatory investigations, enforcement notices requiring us to stop or change the way we use personal data and/or fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims for financial or non-financial loss by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill.

These laws, rules and regulations evolve frequently and their scope may continually change, through new legislation, amendments to existing legislation and changes in enforcement, and may be inconsistent from one jurisdiction to another. The interpretation and application of consumer, health-related and data protection laws, especially with respect to genetic samples and data, in the United States, the European Union (EU) and elsewhere, are often uncertain, contradictory and in flux. As a result, implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future, and we cannot determine the impact such future laws, regulations and standards may have on our business. Our internal computer systems, or those used by our clinical investigators, contractors or consultants, may fail or suffer security breaches.

We are a party to certain agreements that contain liability or indemnification provisions under which we may claim damages from our counterparties and under which our counterparties may claim damages from us, including damages caused by product defects.

We are a party to certain agreements, including clinical trial agreements and licensing agreements that contain liability or indemnification provisions under which we or the counterparty may claim damages. In the event we need to claim damages from a counterparty, we may not receive payments covering our damages in full, either because the applicable provision is unenforceable for any reason or because the counterparty is unable to pay (due to insolvency or otherwise). Although in many

cases we try to limit our liability, such limitations may not be enforceable in certain jurisdictions or effective in the event that we need to pay damages and we nevertheless could become liable to make substantial payments. If we must make substantial liability payments under an agreement, this could have a material adverse effect on our business, results of operations, financial condition and prospects.

Risks Related to the Commercialization of Our Product Candidates

If we are unable to commercialize our product candidates PHVS416 and PHVS719 or any other product candidates that we may pursue, or experience significant delays in doing so, our business, financial condition, results of operations and prospects would be materially adversely affected.

We do not expect to generate product revenues in the foreseeable future. If our product candidates PHVS416 and PHVS719 or any other program that we may pursue fails, we will have to develop, acquire or license new programs. Our product candidates, as well as any other programs we may pursue, could be unsuccessful if they:

- do not demonstrate acceptable safety or efficacy in preclinical studies or clinical trials or otherwise do not meet applicable regulatory standards for approval;
- generate unacceptable adverse side effects;
- do not offer therapeutic or other improvements over existing or future products used to treat the same conditions;
- are not accepted in the medical community or by insurers, either public or private; or
- are not capable of being produced and delivered to patients in commercial quantities at acceptable costs.

The results of the research and trials to date cannot provide assurance that acceptable efficacy or safety will be shown upon completion of ongoing or planned clinical trials. Also, the results obtained in our PHA-0221121- C001 and PHA-022121-C002 clinical trials may not be comparable to results that may be produced during the further development of our PHA121-containing product candidates. Many products that show promise in proof-of-concept, Phase 1 and/or Phase 2 trials fail in later clinical trials or in a commercial setting. If we are unable to make our product candidates commercially available, or we experience significant delays in doing so, our business, financial condition, results of operations and prospects would be materially adversely affected.

The market opportunities for our product candidates may be smaller than currently anticipated, lowering our potential revenue.

The market opportunities for our product candidates may be smaller than currently anticipated, lowering our potential revenue. We make projections of both the number of people who have HAE, as well as the number of individuals within our target patient population who have the desire to switch to an oral therapy and the potential to benefit from treatment with our product candidates. These projections are derived from scientific literature and patient foundations but are highly contingent on a number of variables that are difficult to predict and may prove to be too high, resulting in a smaller population of patients who are interested in, and could benefit from, our product candidates than we currently anticipate which would result in lower potential revenue. Moreover, if we are successful in developing both PHVS416 and PHVS719, we cannot accurately predict the proportion of patients choosing prophylactic or on-demand only treatment regimens.

Use of our product candidates could be associated with side effects or adverse events.

As with all pharmaceutical products, use of our product candidates could be associated with side effects or adverse events, which can vary in severity and frequency. Side effects or adverse events associated with the use of our product candidates may be observed at any time, including in clinical trials or once a product is commercialized, and any such side effects or adverse events may negatively affect our ability to obtain regulatory approval or market our product candidates. Side effects or adverse events associated with the use of our product candidates could result in a label change, require us to perform additional studies or halt development or sale of these product candidates or expose us to product liability lawsuits, which will harm our business. We may be required by regulatory agencies to conduct additional preclinical or clinical trials regarding the safety of our product candidates, which we have not planned or anticipated. We cannot provide any assurance that we will resolve any issues related to any product-related side effects or adverse events to the satisfaction of the FDA or any regulatory agency in a timely manner or ever, which could harm our business, prospects and financial condition.

If we are successful in commercializing our product candidates, the FDA and other comparable foreign regulatory authorities require that we analyze and report certain information about adverse events that our products may have caused or contributed to. The FDA and other foreign regulatory authorities impose strict requirements with respect to the analysis of such events and the manner and timing of our reporting the information to the regulatory authorities. We may fail to comply with the requirements for assessing and reporting adverse events and if we fail to comply with these obligations, the FDA or other comparable foreign regulatory authorities could take action including the issuance of warning letters or other regulatory correspondence, criminal prosecution, the imposition of civil sanctions, seizure of our products, or delay in approval or clearance of future products.

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

Our product candidates may not be commercially successful. Even if any of our product candidates receive regulatory approval, they may not gain sufficient market acceptance among physicians, patients, healthcare payors or others in the medical community. The commercial success of any of our current or future product candidates will depend significantly on the broad adoption and use of the resulting product by physicians and patients for approved indications. The degree of market acceptance of any of our potential products as may receive marketing authorization will depend on a variety of factors, many of which are outside our control, including:

- demonstration of clinical efficacy and safety compared to other more-established products;
- the limitation of our targeted patient population and other limitations or warnings contained in any approved labeling;
- acceptance of a new drug for the relevant indication by healthcare providers and their patients;
- the pricing and cost-effectiveness of our products, as well as the cost of treatment with our products in relation to alternative treatments and therapies;
- our ability to obtain and maintain sufficient third-party coverage and adequate reimbursement from government healthcare programs, private health insurers and other third-party payors;
- the willingness of patients to pay all, or a portion of, out-of-pocket costs associated with our products in the absence of sufficient third-party coverage and adequate reimbursement;

- any restrictions on the use of our products, and the prevalence and severity of any adverse effects;
- the timing of market introduction of our products as well as competitive drugs;
- the effectiveness of our or any of our potential future collaborators' sales and commercialization strategies; and
- unfavorable publicity relating to the product.

If any products that we may develop fail to achieve market acceptance, we may not be able to generate sufficient revenues. We may make substantial investments in clinical development, manufacturing, supply chain and commercialization without any assurance that we will be able to attain significant market share at a price that would enable us to recover our investments. If we are unable to do so, our business, financial condition, results of operations and prospects would be materially adversely affected.

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

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. As discussed under chapter 2 of this report, there are several licensed therapies for HAE and we are aware of a number of HAE therapies in clinical development. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products. Generic products are expected to become available over the coming years, potentially creating pricing pressure. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products. This may make it difficult for us to achieve our business strategy of using our product candidates in combination with existing therapies or replacing existing therapies with our product candidates. Competition may further increase as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries.

Many of the companies against which we are competing or we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites

and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

We may encounter difficulties in managing our growth and expanding our operations successfully.

If we advance our product candidates through clinical trials and regulatory approvals, we will need to expand our development, manufacturing, regulatory, commercialization and supply chain capabilities or contract with third parties to provide these capabilities for us. Our ability to realize our commercialization strategy and manage any growth will require us to continue to recruit and train additional qualified personnel and make appropriate changes to our operational, financial and management controls. We may experience a delay in becoming aware of certain issues or information material to management decisions. The expansion of our operations, including potential expansion into global markets outside of the European Union and the United States, may lead to significant costs, new challenges and risks and may divert the attention of our management and our business development resources. Any inability to manage anticipated growth and expanding operations, including as a result of failing to realize our commercialization strategy for our product candidates PHVS416 and PHVS719, could adversely affect our business, financial condition, results of operations or prospects.

Governments and/or pricing authorities, especially in the European Union, often impose strict price and access controls, which may adversely affect our future profitability.

In some markets, especially in the European Union, prescription drug pricing is subject to governmental/ pricing authority control which can vary by country and degree. In these countries, pricing negotiations with governmental/pricing authorities can take considerable time after the receipt of marketing approval for a product. If reimbursement of any future products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels or the pricing negotiation is considerably delayed, we may be unable to achieve or sustain profitability.

Drug pricing and other healthcare costs continue to be subject to intense political and societal pressures, which we anticipate will continue and escalate on a global basis. These pressures may result in harm to our business and reputation, cause the market price of our ordinary shares to decline or experience periods of volatility and adversely affect results of operations and our ability to raise funds.

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

The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new medicines

are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products.

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 product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medicines, 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.

Moreover, increasing efforts by governmental and third-party payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products into the healthcare market.

In addition, many private payors contract with commercial vendors who sell software that provide guidelines that attempt to limit utilization of, and therefore reimbursement for, certain products deemed to provide limited benefit to existing alternatives. Such organizations may set guidelines that limit reimbursement or utilization of our products.

We may become exposed to costly and damaging liability claims, either when testing our product candidates in the clinic or after commercialization; and our product liability insurance may not cover all damages from such claims.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. Physicians and patients may not comply with any warnings that identify known potential adverse effects and patients who should not use our products. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to stop development or, if approved, limit commercialization of our product candidates. Even successful defenses would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- delay or termination of clinical trials;
- injury to our reputation and negative publicity;
- withdrawal of clinical trial participants, patients or clinical investigators;
- initiation of investigations by regulators or ethics committees;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- decreased demand for our product candidates;
- product recalls or withdrawals, or labeling, marketing or promotional restrictions;
- loss of revenues from product sales;
- the inability to commercialize any of our product candidates, if approved; and
- a decline in the price of our ordinary shares.

Any product liability insurance coverage we obtain may not fully cover potential liabilities that we may incur. Our insurance policies have various exclusions, and we may be subject to a product liability claim for which we have no coverage. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

We will also need to increase our insurance coverage if we commercialize any product that receives marketing approval. Insurance coverage is becoming increasingly expensive. If we are unable to maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could harm our business, financial condition, results of operations and prospects.

If we are unable to establish commercial capabilities or enter into agreements with third parties to market, sell and distribute our product candidates, we may be unable to generate any revenues if and when our product candidates are approved.

If any of our product candidates receive marketing approval, we intend to market, sell and distribute them using our own commercial infrastructure. However, we have no experience in commercialization, selling and distributing pharmaceutical products or establishing a commercial organization. We may enter into collaborations with other entities to utilize their mature sales, marketing and distribution capabilities, but we may be unable to enter into commercialization agreements on favorable terms, if at all. If our future collaborative partners do not commit sufficient resources to commercialize our product candidates, if approved, or if we are unable to develop the necessary commercialization capabilities on our own, we will be unable to generate sufficient product revenues to sustain our business. Further, we may not have sufficient control or oversight over our future collaborative partners to ensure they sell and market our product candidates in compliance with all applicable law. In building our commercial infrastructure or commercializing our product candidates, if approved, we will be competing with other well-funded companies that currently have or are building extensive commercial operations. Without an internal team or the support of a third-party to perform commercial functions, we may be unable to successfully commercialize our product candidates, if approved, and/or compete successfully against these companies.

Risks Related to Our Reliance on Third Parties and Key Personnel

If third parties on which we depend to conduct our clinical trials do not perform as contractually required, fail to satisfy regulatory or legal requirements or miss expected deadlines, our development program could be delayed with materially adverse effects on our business, financial condition, results of operations and prospects.

We rely on CROs, independent clinical investigators, clinical data management organizations, consultants and other third-party firms to design, conduct, supervise and monitor clinical trials. We and these third parties are required to comply with extensive regulations, including good clinical practices, or GCP, which are enforced by the competent authorities of the member states of the European Economic Area, or EEA, the FDA and other comparable regulatory authorities; GCP are intended to ensure that the health, safety and rights of patients are protected in clinical development and clinical trials, and that trial data integrity is assured. In fact, as sponsor of the clinical trials, GCP compliance remains our responsibility. Regulatory authorities ensure compliance with these requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. If we or any of these third parties fail to comply with applicable requirements, clinical trials may be put on "clinical hold," the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with such requirements. In addition, our clinical trials must be conducted with products that are cGMP produced. Failure to comply with these regulations may result in a clinical hold or require us to repeat preclinical and clinical trials, which would delay the regulatory approval process.

Third-party staff are not our employees and, except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical and preclinical programs and meet their quality and other requirements. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines or if the quality or accuracy of the product or clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be put on hold, extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our operations and the commercial prospects for our product candidates in development would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Because we have relied on third parties, our internal capacity to perform these functions is limited. Outsourcing these functions involves the risk that third parties may not perform to our standards, may not produce results in a timely manner or may fail to perform at all. In addition, the use of third-party service providers requires us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated. We currently have a small number of employees, which limits the internal resources we have available to identify and monitor our third-party providers. To the extent we are unable to identify and successfully manage the performance of third-party service providers in the future, our business may be adversely affected. Though we carefully manage the relationships with third parties, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse

impact on our business, financial condition, results of operation and prospects.

If we cannot contract with acceptable third parties on commercially reasonable terms, or at all, or if these third parties do not carry out their contractual duties, satisfy legal and regulatory requirements for the conduct of preclinical studies or clinical trials or meet expected deadlines, our clinical development programs could be delayed and otherwise adversely affected. Any such event could have a material adverse effect on our business, financial condition, results of operations and prospects.

We are dependent on the services of our management and other clinical and scientific personnel, and if we are not able to retain these individuals or recruit additional management or clinical and scientific personnel, our business will suffer.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified management, clinical and scientific personnel. We are highly dependent upon our senior management team as well as our senior scientists. The loss of services of any of these individuals could delay or prevent the successful development of our product candidates, initiation or completion of our planned clinical trials or the commercialization of our product candidates. Our industry has experienced a high rate of turnover of management, clinical and scientific personnel in recent years and despite our efforts to retain valuable employees, members of our management, scientific and development teams may terminate their employment with us. In addition, as we expand our operations, we may not be successful in maintaining our unique company culture and continuing to attract or retain qualified management and scientific and clinical personnel in the future due to the intense competition for qualified personnel among pharmaceutical, biotechnology and other businesses. Replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. If we do not have sufficient numbers of skilled employees to support our research, development, manufacturing, regulatory compliance or management functions, or if our employees lack the skills necessary for the development of our operations, we may need to retain consultants and advisers, if available on terms acceptable to us, if at all, who may have conflicts of interest or other commitments, such as consulting or advisory contracts with other organizations that may affect their ability to contribute to us. In addition, if we are not able to attract, integrate, retain and motivate sufficient scientific, technical and managerial personnel, we will be unable to advance our clinical programs or expand our business, which may have a material adverse effect on our business, financial condition, results of operations and prospects.

We are heavily dependent on third parties to perform critical activities related to the research, development and manufacturing of our product candidates. If these third parties fail or are unable to perform, our development programs and candidate products could be materially and adversely affected and our business and prospects will suffer.

We are heavily dependent on third parties to conduct certain key activities relating to the research, development and manufacturing of our product candidates. For example, we rely on third-party firms to conduct development, studies, and trials with respect to our candidate products and to manufacture and supply the material used in our studies and trials.

Our reliance on third parties may pose the following risks to us:

- third parties have significant discretion in determining the efforts and resources that they will apply to our development programs and product candidates;
- third parties could independently develop, supply, manufacture, commercialize or collaborate with additional third parties, products that compete directly or indirectly with our product candidates;
- third parties may not properly prosecute, maintain, enforce or defend our intellectual property rights or may use our proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation, or other intellectual property proceedings;
- disputes may arise with respect to ownership of any intellectual property developed pursuant to our collaborations and activities with third parties;
- disputes may arise between us and our third-party collaborators and service provider that cause the delay or termination of the development, manufacturing, supply or commercialization of our product candidate, or that result in costly litigation or arbitration that diverts management's attention and resources; and
- if a current or future third-party collaborator or service provider of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

As a result, if any third-parties upon which we are dependent fail or are unable to perform, our development programs and candidate products could be materially adversely affected.

We may be unable to enter into or maintain strategic alliances or collaborations which could affect our ability to commercialize our product candidates, if approved.

We may seek strategic alliances or collaborations to further the clinical development and commercialization of certain of our product candidates as they would likely require expensive and time-consuming clinical trials. In seeking strategic partners, we face significant competition from other companies as well as public and private research institutions. There can be no assurance that we will be able to enter into or maintain strategic alliances on terms favorable to us, or at all. Potential partners may require royalty or milestone payments, rights to current or after-developed intellectual property, exclusivity rights, limitations on liabilities, indemnities or other provisions that are adverse to us. Potential partners may fail to diligently fund, develop or commercialize our product candidates. Any of the foregoing may have a material adverse effect on our business, financial condition, results of operations and prospects.

Risks Related to Our Intellectual Property

If we fail to make required payments to AnalytiCon pursuant to the agreements pursuant to which we acquired certain of our core intellectual property or are otherwise in material breach of such agreements (and fail to cure such breaches within a specified time period), AnalytiCon may exercise remedies pursuant to such agreements that would materially and adversely affect our business and results of operations.

Certain intellectual property that is core to our business has been invented by AnalytiCon and

contractually assigned to us by AnalytiCon, with whom we continue to collaborate for the development of our product candidates. We owe AnalytiCon milestone payments contingent on our achievement of certain clinical development and regulatory events, as well as royalties and milestone payments based on sales of such product candidates. If we fail to make such payments to AnalytiCon or are otherwise in material breach of certain agreements that we entered into with AnalytiCon (and fail to cure such breaches within a specified time period), and AnalytiCon exercises contractual remedies available to it under such agreements, then we may be required to grant AnalytiCon an exclusive license to the intellectual property that it assigned to us for use in all applications, including HAE. In addition, we could be prevented from competing with AnalytiCon until five years after the commercial launch of any product candidates containing a compound from the OB2RA Class. If we failed to make such payments and AnalytiCon were to exercise such remedies, we would not be able to continue our current development program or commercialize our product candidates and our business and results of operations would be materially and adversely affected. For a description of our arrangement with AnalytiCon, please see chapter 2 of this report.

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

Our commercial success depends in significant part on obtaining and maintaining current and future patent protection, trade secrets and confidential know-how for our technologies, product candidates, the methods used to manufacture those product candidates and the methods for treating patients using those product candidates. We may not be able to file, prosecute, maintain, enforce, or license all necessary or desirable patents and patent applications at a reasonable cost or in a timely manner. Our failure to obtain, maintain or extend patent protection or to protect trade secrets or confidential know-how could materially adversely affect our ability to compete.

Obtaining and enforcing patents in the pharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and subject to numerous risks and uncertainties. These risks and uncertainties include, but are not limited, to the following:

- the United States Patent and Trademark Office, or USPTO, and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process, the noncompliance with which can result in abandonment or lapse of a patent or patent application, and partial or complete loss of patent rights in the relevant jurisdiction;
- patent applications may not result in any patents being issued;
- patents may be challenged, invalidated, modified, revoked, circumvented, found to be unenforceable or otherwise may not provide any competitive advantage;
- our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with or block our ability to make, use and sell our product candidates;
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of patent protection both inside and outside the United States for disease

treatments that prove successful, as a matter of public policy regarding worldwide health concerns; and

- countries other than the United States may have patent laws less favorable to patentees than those upheld by U.S. courts, allowing foreign competitors a better opportunity to create, develop and market competing products.

If we or any third parties that develop or create any intellectual property for us are unable to secure necessary assignments or rights, then our rights to such intellectual property, and ultimately our ability to protect our candidate products, may be adversely affected.

It is also possible that we fail to identify patentable aspects of our research and development output in time to obtain patent protection. In addition, we may not be aware of all third-party intellectual property rights potentially relating to our product candidates and technology. We cannot guarantee that any of our or our licensors' patent searches or analyses, including but not limited to the identification of relevant patents, analysis of the scope of relevant patent claims or determination of the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the United States and elsewhere that is relevant to or necessary for the development and commercialization of our product candidates in any jurisdiction. For example, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in any licensed patents or pending patent applications (or claimed in any patents that we may own in the future, if any), or that we were the first to file for patent protection of such inventions.

The duration and scope of any patents we are issued in the future (if any) or the patent rights of our licensors or collaborators may not be sufficient to effectively protect our product candidates and business.

The patent position of biopharmaceutical companies generally is highly uncertain, involves complex legal and factual questions, and has been the subject of much litigation in recent years. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Even if our current or future patent applications are issued as patents, they may not be issued with the scope of claims sought by us, or the scope of claims we or our licensors are seeking may not be sufficiently broad to protect our product candidates or provide us with any competitive advantage. Any patents that we may own in the future (if any) may be challenged or circumvented by third parties or may be narrowed or invalidated as a result of challenges by third parties. Consequently, we do not know whether our product candidates will be protectable by valid and enforceable patents.

Moreover, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Changes in or different interpretations of patent laws in the United States, Europe, and other jurisdictions may also permit others to use our discoveries or to develop and commercialize our technology and products without providing any compensation to us, or may limit the number of patents or claims we can obtain. The laws of some countries do not protect intellectual property rights to the same extent as U.S. and European laws and those countries may lack adequate rules and procedures for defending our intellectual property rights.

Our competitors and other third parties would be able to offer and sell products so long as they do not infringe any valid and enforceable patents or other proprietary rights that we or others, including

our licensors, may have. The specific content of patents and patent applications that are necessary to support and interpret the scope of patent claims is highly uncertain due to the complex nature of the relevant legal, technical and factual issues. Such risks will increase if we or our licensors are not able to obtain additional patents protecting aspects of our product candidates and technology, such as product improvements, formulations, methods of production or novel uses of the relevant product candidates.

In addition, patents have a limited lifespan. For example, if renewal fees are paid timely, a European patent expires 20 years after its effective filing date. Similarly, if all maintenance fees are timely paid, a patent in the United States generally expires 20 years after its effective filing date. Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop in the United States, any patents we are issued in the future (if any) may qualify for a limited patent term extension if certain criteria are met (e.g., in case of significant delays during patent prosecution or during FDA approval for bringing a drug covered by a patent to market) under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. Specifically, the Hatch Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, in such an event we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. In the European Union, an extension of the duration of protection for a pharmaceutical product on the basis of a supplementary protection certificate could be applied for after a valid market authorization is obtained and if the product is specifically covered by a basic patent in force. As a result, an additional term of protection could be obtained for the relevant product on top of the maximum lifespan of the patent. The term of the allowed extension varies, and in principle is at most five and a half years. Consequently, despite these general possibilities for obtaining a certain extension of the duration of protection based on a patent if certain criteria are met, the protection provided by a patent is limited in time.

Furthermore, given the amount of time required for the development, testing, and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Even if additional patents covering our product candidates are obtained, the expiration of a patent may leave us more vulnerable to competition from biosimilar or generic alternatives, and our business, financial condition, results of operations and prospects could be materially harmed. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

Patents covering our technology and product candidates that may be issued (if any) could be found invalid or unenforceable if challenged in court or an issuing body.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and any patents we may own in the future (if any) may be challenged in the courts or patent offices in the United States and elsewhere. Such challenges may result in loss of exclusivity or in patent claims

being narrowed, invalidated or held unenforceable which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product candidates.

To the extent that we obtain any patents in the future, our patent protection in respect of our product candidates and technologies may be limited or lost if patents that may be issued to us or patents we use under the terms of exclusive commercial licenses were to be declared invalid, rendered unenforceable or narrowed in scope as a result of any re-examination, post grant review, inter partes review, interference proceedings, derivation proceedings, equivalent proceedings in other jurisdictions or judicial action. If one of our licensing partners or we initiate legal proceedings against a third-party to enforce a patent covering one of our product candidates or technologies, the defendant could counterclaim that the patent covering our product candidate is invalid or unenforceable. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, lack of patentable subject matter, lack of written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the relevant issuing body, or made a misleading statement, during prosecution. A challenge to patents could result in a ruling adverse to us that could invalidate or render unenforceable such patents or substantially reduce the scope of protection afforded by them. A court may also determine, retrospectively, that despite the issuance of the patent by the relevant issuing body, the corresponding patent application did not meet the statutory requirements. If a competitor or other third parties were to successfully challenge our patents (to the extent any are obtained), and claims in these patents were consequently narrowed, rendered unenforceable or invalidated, our ability to protect the related product candidate or technology from competition could be compromised. Such proceedings could result in the revocation or cancellation of or amendment to such patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensing partners were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our product candidates to the extent that any such patents are issued. Such a loss of patent protection could have a material adverse impact on our business.

We may not be able to protect or enforce our intellectual property rights in all jurisdictions.

Filing, prosecuting, and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States or the European Union. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries, or from selling or importing products made using our inventions in and into the United States, the European Union or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and may export otherwise infringing products and these products may compete with our product candidates in jurisdictions where we do not have any issued patents.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. Patent laws vary by jurisdiction, and, accordingly, the degree of protection afforded to the same technology, if any, may differ depending on the jurisdiction. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of

patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of any patents we are issued in the future (if any) or commercialization of competing products in violation of our proprietary rights generally. Proceedings to enforce any patent rights we are issued in the future (if any) in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put such patents at risk of being invalidated or interpreted narrowly and could provoke third parties to assert claims against us. In such an event, we may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license. Our inability to protect or enforce our intellectual property rights throughout the world could have a material adverse effect on our business, prospects, financial condition, results of operations and prospects.

In addition, many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties and many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we (to the extent we are issued any patents covering our product candidates) or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

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

To the extent that we are issued patents covering our product candidates (if any), changes in either patent laws or interpretations of patent laws in the United States, the European Union, Canada or other jurisdictions may diminish the value of our intellectual property or narrow the scope of our patent protection and could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents (to the extent any such patents are issued).

For example, patent reform legislation in the United States, including the Leahy-Smith America Invents Act, or the America Invents Act, could increase those uncertainties and costs. The America Invents Act was signed into law on September 16, 2011, and many of the substantive changes became effective on March 16, 2013. The America Invents Act reforms United States patent law in part by changing the U.S. patent system from a "first to invent" system to a "first inventor to file" system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third-party was the first to invent the claimed invention. In addition, the America Invents Act expands the definition of prior art and develops a post-grant review system. This legislation changed United States patent law in a way that may weaken our ability to obtain patent protection in the United States for those applications filed after March 16, 2013.

Further, the America Invents Act created new procedures to challenge the validity of issued patents in the United States, including post grant review, inter partes review, and derivation proceedings, which some third parties have been using to cause the cancellation of selected or all claims of issued patents. These adversarial actions at the USPTO review patent claims without the presumption of validity afforded to U.S. patents in lawsuits in U.S. federal courts, and use a lower burden of proof than used in litigation in U.S. federal courts. Therefore, it is generally considered easier for a competitor or third-party to have a U.S. patent invalidated in a USPTO post-grant review or inter partes review

proceeding than invalidated in a litigation in a U.S. federal court. If any patents that we are issued in the future (if any) or our licensor's patents are challenged by a third- party in such a USPTO proceeding, there is no guarantee that we or our licensors or collaborators will be successful in defending the patent, which would result in a loss of the challenged patent right to us.

In addition, the patent positions of companies in the development and commercialization of pharmaceuticals are particularly uncertain. Recent court rulings in cases such as Association for Molecular Pathology v. Myriad Genetics, Inc., BRCA1- &BRCA2-Based Hereditary Cancer Test Patent Litigation, Mayo Collaborative Services v. Prometheus Laboratories, Inc., Promega Corp. v. Life Technologies Corp. and Abbvie Deutschland GmbH v. Janssen Biotech, Inc. have narrowed the scope of patent protection available in certain circumstances and weakened 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 events has created uncertainty with respect to the value of patents once obtained. Depending on future actions by the U.S. Congress, the U.S. courts, and the USPTO and the relevant law-making bodies in other countries, 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 might obtain in the future. Any changes to patent law in the U.S. or other jurisdictions that impairs our ability to protect our PHA121 and other product candidates that we may pursue could have a material adverse effect on our business, financial condition, results of operations and prospects.

Confidentiality agreements with employees and third parties may not prevent unauthorized disclosure of trade secrets and other proprietary information and may not provide an adequate remedy.

We consider proprietary trade secrets and confidential know-how and unpatented know-how to be important to our business. We rely on trade secrets and confidential know-how to protect our technology, especially where we do not believe that patent protection is appropriate or obtainable. However, trade secrets and confidential know-how are difficult to protect and some courts in the United States, the European Union and elsewhere are less willing or unwilling to protect trade secrets. We seek to protect our proprietary trade secrets and confidential know-how, in part, by entering into confidentiality agreements with our current and former employees, consultants, contractors, outside scientific collaborators and other advisers. However, we cannot guarantee that we have entered into such agreements with each party that may have or has had access to our trade secrets or confidential know-how or that such agreements will fully protect our proprietary trade secrets and confidential know-how. Our current or former employees, consultants, contractors, outside scientific collaborators and other advisers may have access to and unintentionally or willfully disclose our confidential information, including to competitors. Our confidentiality agreements may be breached by such individuals and we may not have adequate remedies for any breach. Enforcing a claim that a third-party obtained illegally and is using trade secrets and confidential know-how illegally is expensive and time consuming and the outcome is unpredictable. Failure to obtain or maintain trade secret and confidential know-how trade protection could adversely affect our competitive business position. Moreover, our competitors and other third parties may independently develop equivalent knowledge, methods and know-how and may even apply for patent protection in respect of the same. If successful in obtaining such patent protection, our competitors could limit how we use our trade secrets and confidential know-how, which may have a material adverse effect on our business, financial condition, results of operations and prospects.

If we or our licensors infringe, misappropriate or otherwise violate intellectual property rights of third parties, we may face increased costs or we may be unable to commercialize our product candidates.

Our commercial success depends upon our ability to develop, manufacture, market, sell and distribute our product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. There is a risk that third parties may allege that our employees, consultants, independent contractors or the licensors have wrongfully used or disclosed trade secrets and we infringed, are infringing, or will infringe the proprietary rights of third parties because patents and pending applications belonging to third parties exist in the European Union, the United States and elsewhere in the world in the areas in which our research is conducted. Because patent applications take several years to complete, there may be currently pending applications, unknown to us, which may later result in issued patents that cover the production, manufacture, commercialization or use of our product candidates and technology. In addition, the production, manufacture, commercialization or use of our product candidates may infringe existing patents of which we are not aware. Even if we believe such claims of infringement are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could materially and adversely affect our ability to commercialize our product candidates and technology. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. Even if we are successful in defending against such claims, litigation could be time-consuming and result in substantial costs and be a distraction to management.

If we are found to infringe a third-party's valid and enforceable intellectual property rights, we could be required to:

- cease developing, manufacturing, selling or licensing the infringing product candidates or technology;
- obtain a license from such third-party to continue developing, manufacturing and marketing our product candidates and technologies, which may not be available on commercially reasonable terms or at all and even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments or grant a cross license to our patents (to the extent any such patents are issued) to another patent holder;
- pay substantial damages for past infringement, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right; or
- be required to redesign the formulation of a product such that it does not infringe, which may not be possible or could require substantial funds and time.

Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

We have received proprietary information and know-how from third parties. In addition, many

of our employees were previously employed at other biotechnology or pharmaceutical companies. Although we try to ensure that our employees, consultants, and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. We may be subject to ownership disputes in the future arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates. We may also be subject to claims that former employees, consultants, advisors or other third parties have an ownership interest in our patents or other intellectual property. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could have a material adverse effect on our business, financial condition, results of operations and prospects, and be a distraction to our management and employees.

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

To the extent that we are issued any patents covering our product candidates, competitors may infringe such patents or the patents of our licensing partners. However, we may not have the resources to reliably detect infringements of intellectual property rights, and even if we detect an infringement we may not be able to trace the source of the infringement, or uphold our rights. We may need to resort to litigation to enforce our intellectual property rights, including any patents issued to us (if any) or our licensors. If a competitor or other third-party files a patent application claiming technology also invented by us, in order to protect our rights, we may have to participate in an expensive and time-consuming opposition proceeding before the European Patent Office, the USPTO or patent authorities or courts in other jurisdictions, with an uncertain outcome and which may have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, our success depends in part on avoiding the infringement of other parties' patents and other intellectual property rights as well as avoiding the breach of any licenses relating to our technologies and products. In the United States, patent applications filed in recent years are confidential for 18 months, while older applications are not published until the patent issues. As a result, avoiding patent infringement may be difficult and we may inadvertently infringe third-party patents or proprietary rights. Countering infringement or unauthorized use claims or to defend against such claims and challenges can be expensive and time consuming. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our ordinary shares.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, commercialization or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

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

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or applications will be due to be paid to various patent agencies over the lifetime of our licensed patents and/or applications and any patent rights we may own in the future. Patent agencies also require compliance with several procedural fee payments and other similar provisions during the patent application process. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market and this circumstance could have a material adverse effect on our business.

We may not be successful in obtaining necessary rights to any product candidates we may develop through acquisitions and licenses.

Many pharmaceutical companies, biotechnology companies, and academic institutions are competing with us and filing patent applications potentially relevant to our business. If patents issued to third parties contain valid claims that cover our product candidates or their manufacture or uses or assays relevant to our development plans, in order to avoid infringing these patents, we may be required or find it prudent to obtain licenses to these patents or to develop or obtain alternative technology. However, we may be unable to secure such licenses or otherwise acquire or license any compositions, methods of use, processes, or other intellectual property rights from third parties that we identify as necessary for product candidates we may develop. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third- party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate.

In addition, if a patent is issued to a third-party that covers our product candidates or their manufacture or uses or assays related to our technology or product candidates and we cannot obtain a license to such patent, then we may not be in a position to commercialize such technology or product candidates unless we develop non-infringing alternative or successfully pursue litigation to have that patent invalidated or enter into a licensing arrangement with the patent holder. Any such litigation would be time consuming and costly, and the outcome would not be guaranteed. We cannot be certain that we would be able to enter into a licensing agreement with the patent holder on commercially reasonable terms, if at all. In either case, our business prospects could be materially adversely affected.

Intellectual property rights do not necessarily address all potential risks to our competitive advantage.

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

- others may be able to make products that are similar to any product candidates we may develop or utilize similar technology but that are not covered by the claims of the patents that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent (if any) or pending patent application that we license or may own in the future;
- we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that patent applications that we currently, or may in the future, own or license will not lead to issued patents;
- the claims of patents or patent applications that we may own or license may, when issued, not cover our product candidates;
- issued patents (if any) that we may hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third- party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and prospects.

Risks Related to Our Business and Industry

Our relationships with health care professionals, institutional providers, principal investigators, consultants, customers and third-party payors are, and will continue to be, subject, directly and indirectly, to laws and regulations on health care fraud and abuse, false claims, commercialization expenditure tracking and disclosure, and health information privacy and security. If we are unable to comply, or have not fully complied, with such laws, we could face penalties, including, without limitation, civil, criminal, and administrative penalties, damages, fines, exclusion from government-funded health care programs and the curtailment or restructuring of our operations.

Although we do not currently have any products on the market, our business operations and activities may be directly or indirectly subject to various laws and regulations on health care fraud and

abuse, false claims, commercialization expenditure tracking and disclosure, and health information privacy and security. If we obtain approval for any of our product candidates from the FDA or comparable other regulatory authorities and begin commercializing those products in geographies for which they have been approved, our potential exposure under such laws will increase significantly, and our costs associated with compliance with such laws are also likely to increase. These laws may impact, among other things, our current activities with principal investigators and research subjects, as well as proposed and future sales, marketing and education programs.

The laws that may affect our ability to operate include, but are not limited to:

- the federal Anti-Kickback Statute, which is an intent-based federal criminal statute that prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing any remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease, order, recommendation or arranging of, any item or service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare and Medicaid;
- the federal civil False Claims Act, which imposes civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment to a federal health care program or knowingly making using or causing to be made or used a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government;
- the federal criminal statute on false statements relating to health care matters, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of or payment for health care benefits, items or services;
- the federal criminal health care fraud statute, enacted as a part of the Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for executing, or attempting to execute, a scheme or artifice to defraud any health care benefit program or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any health care benefit program in connection with the delivery of or payment for healthcare benefits, items, or services;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and their respective implementing regulations, which impose requirements on certain covered health care providers, health plans, and health care clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization;
- laws in all 50 U.S. states require businesses to provide notice to customers whose personally identifiable information has been disclosed as a result of a data breach, and certain U.S. state laws impose particular requirements relating to the handling of sensitive data, such as health information;
- the federal Physician Payments Sunshine Act that requires "applicable manufacturers" of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program, among others, to track and report

annually to the Department of Health and Human Services (for disclosure to the public) information related to certain payments and other transfers of value to "covered recipients", which includes U.S.-licensed physicians, teaching hospitals and, for reports submitted on or after January 1, 2022, physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse midwives;

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers;
- the Foreign Corrupt Practices Act, or the FCPA, a U.S. law which regulates certain financial relationships with foreign government officials which could include, for example, certain medical professionals;
- analogous U.S. state law equivalents to the above federal laws, such as analogous state laws to the Anti-Kickback Statute and the False Claims Act, which may apply to items and services reimbursed by any third-party payor, including commercial insurers (i.e., so-called "all-payor anti-kickback laws");
- U.S. state laws regulating pharmaceutical manufacturer compliance programs, commercialization- related activities, drug price transparency disclosures, and other practices; and
- analogous foreign laws and regulations.

The Affordable Care Act, among other things, amended the intent standard of the federal Anti-Kickback Statute and criminal health care fraud statutes to a stricter standard such that a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. In addition, the Affordable Care Act codified case law that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act.

Efforts to ensure that our business arrangements will comply with applicable health care laws may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations, guidance or case law interpreting applicable fraud and abuse or other health care laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face penalties, including, without limitation, civil, criminal, and administrative penalties, damages, fines, exclusion from government funded health care programs, such as Medicare and Medicaid, disgorgement, reputational harm, additional oversight and reporting obligations pursuant to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with applicable laws and regulations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to market our products, if approved, and adversely impact our financial results. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws and regulations, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management's attention from the operation of our business, even if our defense is successful. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, it may be costly to us in terms of money, time and resources, and they may be subject to criminal, civil or administrative sanctions, including exclusions from government-funded healthcare programs.

In addition, the regulatory approval and commercialization of any of our product candidates

outside the United States will also likely subject us to foreign equivalents of the health care laws mentioned above, among other foreign laws.

Rapid technological change could make our product candidates or technologies obsolete.

Pharmaceutical technologies and products are subject to rapid and significant technological change. We expect our competitors and physicians will develop new technologies, protocols and products that may render our product candidates and drug formulation technologies uncompetitive or obsolete. The products, protocols and technologies of our competitors and physicians may be more effective than the products, product candidates and drug formulation technologies developed by us. As a result, our product candidates may become obsolete before we recover expenses incurred in connection with their development or realize revenues from any commercialized product. We are aware of other pharmaceutical companies that are developing competing technologies, which could render our product candidates obsolete, which would have a material adverse effect on our business, financial condition, results of operations and prospects.

Our business may become subject to economic, political, regulatory and other risks associated with international operations.

Our business is subject to risks associated with conducting business internationally. Many of our suppliers and collaborative and clinical trial relationships are located in different countries. Accordingly, our future results could be harmed by a variety of factors, including, but not limited to:

- economic weakness, including inflation, or political instability in particular economies and markets;
- differing regulatory requirements for drug approvals in different jurisdictions;
- differing jurisdictions could present different issues for securing, maintaining and/or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with laws and regulations;
- changes in regulations and customs, tariffs and trade barriers;
- changes in currency exchange rates of the euro and currency controls;
- changes in a specific country's or region's political or economic environment;
- trade protection measures, import or export licensing requirements or other restrictive actions by various governments;
- differing reimbursement regimes and price controls in certain markets;
- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and

  business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

If we do not achieve our projected development goals in the timeframes we announce and expect, the commercialization of our products may be delayed and, as a result, our stock price may decline.

From time to time, we estimate the timing of the anticipated accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones are and will be based on numerous assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If we do not meet these milestones as publicly announced, or at all, the commercialization of our products may be delayed or never achieved and, as a result, our stock price may decline.

Risks Related to Legal Compliance Matters

Because we and our suppliers are subject to environmental, health and safety laws and regulations, we may become exposed to enforcement, liability and substantial expenses in connection with environmental compliance or remediation activities which may adversely affect our business and financial condition.

Our operations, including our research, development, testing and manufacturing activities, are subject to numerous environmental, health and safety laws and regulations, and possible permit obligations. These laws, regulations, including any permit obligations, govern, among other things, the controlled use, storage, handling, release and disposal of, and the maintenance of a registry for, hazardous materials and biological materials (goods and substances), chemicals, biological materials and biotechnology. Our operations produce hazardous waste products. We contract with licensed third parties for the disposal of these materials, substances and wastes. Apart from compliance with the applicable regulations, we may not be able to eliminate the risk of contamination or injury from these materials completely. In the event of contamination or injury resulting from any use of hazardous materials, we could be held liable for any resulting damages. We also could incur significant costs associated with civil, administrative and/or criminal fines and penalties for failure to comply all of these laws, regulations, and associated compliance activities.

The third parties with whom we contract to manufacture our product candidates are also subject to these and other environmental, health and safety laws and regulations. Liabilities they incur pursuant to these laws and regulations or any violations thereof could result in significant costs, significant administrative, civil and/or criminal fines, measurements and/or sanctions, or in certain circumstances, an interruption in operations, any of which could adversely impact our business and financial condition, especially if we are unable to find an alternate supplier in a timely manner.

Environmental, health and safety laws and regulations are becoming more stringent and enforcement is prioritized. We may be required to incur substantial expenses in connection with current and future environmental, health and/ or safety compliance, our duty of care in this regard, remediation obligations and/or measurement obligations, in which case, our production and development efforts may be interrupted or delayed and our financial condition and results of operations may be materially adversely affected.

We, our employees, contractors, principal investigators, CROs, consultants, agents, vendors and collaboration partners may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

We are exposed to the risk that we, our employees, contractors, principal investigators, CROs, consultants, agents, vendors and collaboration partners may engage in fraudulent conduct or other illegal activities. Misconduct by these parties could include intentional, reckless and negligent conduct or unauthorized activities that violate, among other things: (i) the legal requirements or other requirements of the FDA and comparable authorities, including those laws that require the reporting of true, complete and accurate information to such authorities; (ii) manufacturing standards; (iii) data privacy, security, fraud and abuse and other healthcare laws and regulations; or (iv) laws that require the reporting of true, complete and accurate financial information and data. In particular, our business activities may be subject to the FCPA and anti-bribery or anti–corruption laws, regulations or rules in other relevant countries for our activities, including the U.K. Bribery Act. The FCPA generally prohibits offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to a non-U.S. government official in order to influence official action, or otherwise obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the corporation and to devise and maintain an adequate system of internal accounting controls. Our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are (directly or indirectly) employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, our dealings with these prescribers and purchasers are subject to regulation under, but not limited to, the FCPA. Recently the SEC and Department of Justice have also increased their FCPA enforcement activities with respect to pharmaceutical companies.

Sales, commercialization and business arrangements in the healthcare industry are generally subject to extensive laws and regulations intended to prevent fraud, misconduct, bribery (e.g. kickbacks), self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws and regulations could also involve the improper use or misrepresentation of information obtained in the course of clinical trials or creating fraudulent data in our preclinical studies or clinical trials, which could result in enforcement and/or sanctions and cause serious harm to our reputation.

Further, we are subject to trade and economic sanctions and embargoes on certain countries, persons, groups, entities, projects and/or activities, and export control regulations, applicable in the United States and other relevant countries for our activities.

There is no certainty that all of our employees, agents, contractors, principal investigators, CROs, consultants, vendors or (other) collaborators, or those of our affiliates, will comply with all applicable laws and regulations, particularly given the high level of complexity of these laws. It is not always possible to identify and deter misconduct by these parties 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, claims or lawsuits stemming from a failure to comply with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could result, among others, in significant administrative, civil and criminal fines, disgorgement,

and other sanctions, remedial measures or consequences, such as the closing down of our facilities, exclusion from participation in federal healthcare programs including Medicare and Medicaid, integrity and compliance oversight and reporting obligations, and prohibitions on the conduct of our business. Any such violations and consequences could materially damage our reputation, our brand, our international expansion efforts, our ability to attract and retain employees, and our business, prospects, operating results and financial condition.

Risks Related to Our Ordinary Shares and Our Status as a Public Company

An active trading market for our ordinary shares may not be sustainable. If an active trading market is not maintained, investors may not be able to resell their shares at or above the offering price and our ability to raise capital in the future may be impaired.

Although our ordinary shares are listed and being traded on Nasdaq, an active trading market for our shares may not be maintained. If an active market for our ordinary shares is not maintained, it may be difficult for you to sell shares you have purchased without depressing the market price for the shares or at all. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

The ownership of our ordinary shares is concentrated and your interests may conflict with the interests of our significant shareholders.

As of April 22, 2021, our significant shareholders beneficially owned ordinary shares representing approximately 54% of our outstanding ordinary shares.

These significant shareholders have in the past often taken a similar position and exercised influence over matters requiring approval of our shareholders or our Board. They may act jointly or independently in the future, and will continue to be able to exert significant influence over the outcome of matters requiring approval of our shareholders or our Board, including but not limited to the approval of significant transactions. Their interests may differ from the interests of other shareholders. Among other consequences, this concentration of ownership may have the effect of delaying or preventing a change in control and might therefore negatively affect the market price of our ordinary shares.

We do not currently intend to pay dividends on our securities and, consequently, your ability to achieve a return on your investment will depend on appreciation in the price of our ordinary shares. In addition, any distribution of dividends must be in accordance with the rules and restrictions applying under Dutch law.

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

Under Dutch law, we may only pay dividends to the extent our shareholders' equity (eigen vermogen) exceeds the sum of the paid-up and called-up share capital plus the reserves required to be maintained by Dutch law or by our Articles of Association and (if it concerns a distribution of profits) after adoption of the annual accounts by our general meeting from which it appears that such distribution is allowed. Subject to such restrictions, any future determination to pay dividends will be at the discretion of the Board and will depend on a number of factors, including our results of operations, earnings, cash flow, financial condition, future prospects, contractual restrictions, capital investment requirements, restrictions imposed by applicable law and other factors considered relevant by the Board.

Under our Articles of Association, if any preferred shares are or have been outstanding, a dividend is first paid out of the profit, if available for distribution, to the holders or former holders, as applicable, of those preferred shares to the extent they are entitled to such distribution under our Articles of Association, which we refer to as our preferred dividend. Our Board may decide that all or part of our remaining profits shall be added to our reserves. After such reservation any remaining profit will be at the disposal of the general meeting at the proposal of our Board for distribution on our ordinary shares, subject to the applicable restrictions of Dutch law. Our Board is permitted, subject to certain requirements, to declare interim dividends without the approval of the general meeting. Dividends and other distributions shall be made payable not later than the date determined by the Board. Claims to dividends and other distributions not made within five years from the date that such dividends or distributions became payable will lapse and any such amounts will be considered to have been forfeited to us (verjaring).

In addition, exchange rate fluctuations may affect the amount of euros that we are able to distribute, and the amount in U.S. dollars that our shareholders receive upon the payment of cash dividends or other distributions we declare and pay in euros, if any. These factors could harm the value of our ordinary shares, and, in turn, the U.S. dollar proceeds that holders receive from the sale of our ordinary shares.

If we do pay dividends, such dividends paid by us on our ordinary shares may be subject to Dutch dividend withholding tax and, if such dividends are paid to certain related parties in low-taxed jurisdictions, might in the future become subject to an additional Dutch withholding tax on dividends, in addition to the applicable Dutch dividend withholding tax.

Under current Dutch tax law, dividends paid by us on our ordinary shares 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.

In a letter to the Dutch parliament dated May 29, 2020, the Dutch State Secretary for Finance announced that the Dutch government intends to introduce an additional withholding tax on dividends paid to related entities (as described below) 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, effective January 1, 2024. On September 25, 2020, the Dutch government launched an internet consultation to give interested parties the opportunity to respond to the draft legislative proposal to introduce the conditional withholding tax on dividends. Pursuant to the proposal published for consultation purposes, the conditional withholding tax on dividend payments will be an addition to the recently passed conditional withholding tax on interest and royalty payments pursuant to the Dutch Withholding Tax Act 2021 (Wet bronbelasting 2021), which act has become effective January 1, 2021. For purposes of the Dutch Withholding Tax Act 2021, generally an entity is considered a related entity if such entity has a "qualifying interest" in us, generally meaning an interest – either individually or

jointly as part of a collaborating group (samenwerkende groep) – that enables the holder of such interest to exercise a decisive influence on the decisions that can determine our activities.

It is possible that the rate will be as high as the highest Dutch corporate income tax rate (currently 25%) 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 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%. The internet consultation closed on October 23, 2020. After the internet consultation, the Dutch government aims to prepare the final legislative proposal in early 2021.

We have broad discretion in the use of our cash on hand and may invest or spend it in way with which you do not agree and in ways that may not yield a return on your investment.

Following the completion of our initial public offering, we had €242.6 million in cash and cash equivalents. Our management will have broad discretion in the use of such cash and could spend it in ways that do not improve our results of operations or enhance the value of our ordinary shares. You will not have the opportunity to influence our decisions on how to use our cash on hand. The failure by our management to apply these funds effectively could result in financial losses that could harm our business, cause the price of our ordinary shares to decline and delay the development of our product candidates. Pending its use, we may invest our cash on hand in a manner that does not produce income or that loses value.

A significant portion of our ordinary shares may be sold into the public market in the near future, which could cause the market price of our ordinary shares to drop significantly, even if our business is doing well.

The market price of our ordinary shares may decline as a result of sales of a large number of our ordinary shares in the market or the perception that these sales may occur. These sales, or the possibility that these sales may occur, also might make it more difficult for us to sell equity securities in the future at a time and at a price that we deem appropriate.

We had a total of 33,128,593 ordinary shares outstanding as of April 22, 2021. Subject to any contractual restrictions under the lock-up agreements entered into in connection with our initial public offering, if our existing shareholders sell substantial amounts of ordinary shares in the public market, or the market perceives that such sales may occur, the market price of our ordinary shares and our ability to raise capital through an issue of equity securities in the future could be adversely affected.

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

As of the date of this report, we are subject to the Dutch Corporate Governance Code, or the DCGC. The DCGC contains both principles and best practice provisions on corporate governance that regulate relations between the Board and the general meeting and matters in respect of financial

reporting, auditors, disclosure, compliance and enforcement standards. The DCGC is based on a "comply or explain" principle. Accordingly, companies are required to disclose in their annual reports, filed in the Netherlands, whether they comply with the provisions of the DCGC. If they do not comply with those provisions (for example, because of a conflicting Nasdaq requirement), the company is required to give the reasons for such noncompliance. The DCGC applies to Dutch companies listed on a government-recognized stock exchange, whether in the Netherlands or elsewhere, including Nasdaq. However, for the fiscal year ended 31 December 2020, the DCGC did not yet apply to the Company. Consequently, the Company does not consider itself to have been bound by the DCGC during the fiscal year ended 31 December 2020 nor to have deviated from any of the principles and best practice provisions of the DCGC in such fiscal year. Similarly, the Company does not consider the disclosure recommendations promulgated by the DCGC with respect to the contents of a listed company's board report to be relevant with respect to this report, because this report pertains to a fiscal year during which the DCGC did not apply to the Company. Nevertheless, these disclosure recommendations have been addressed in this report on a voluntary basis to the extent we believe they are. This may affect your rights as a shareholder and you may not have the same level of protection as a shareholder in a Dutch company that fully complies with the DCGC.

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

We are a "foreign private issuer," as defined in the SEC's rules and regulations. The Nasdaq Listing Rules include certain accommodations in the corporate governance requirements that allow foreign private issuers to follow "home country" corporate governance practices in lieu of the otherwise applicable corporate governance standards of Nasdaq. The application of such exceptions requires that we disclose the Nasdaq Listing Rules that we do not follow and describe the Dutch corporate governance standards, including those as per the DCGC that we do follow in lieu of the relevant Nasdaq corporate governance standard. We intend to continue to follow Dutch corporate governance practices in lieu of the corporate governance requirements of Nasdaq in certain respects.

In accordance with Dutch law and generally accepted business practices, our Articles of Association do not provide quorum requirements generally applicable to general meetings of shareholders. To this extent, our practice varies from the requirement of Nasdaq Listing Rule 5620(c), which requires an issuer to provide in its bylaws for a generally applicable quorum, and that such quorum may not be less than one-third of the outstanding voting stock. Although we must provide shareholders with an agenda and other relevant documents for the general meeting of shareholders, Dutch law does not have a regulatory regime for the solicitation of proxies and the solicitation of proxies is not a generally accepted business practice in the Netherlands, thus our practice will vary from the requirement of Nasdaq Listing Rule 5620(b). As permitted by the listing requirements of Nasdaq, we have also opted out of the requirements of Nasdaq Listing Rule 5610, which requires an issuer to disclose within four business days any waiver of the code of conduct that has been granted to directors and officers. We are also relying on the phase-in provisions of Rule 10A-3 of the Exchange Act and the Nasdaq transition rules applicable to companies completing an initial public offering, which require all members of our audit committee meet the independence standard for audit committee membership within one year of the effectiveness of the registration statement relating to our initial public offering. In addition, we have opted out of shareholder approval requirements, as included in the Nasdaq Listing Rules, for the issuance

of securities in connection with certain events such as the acquisition of shares or assets of another company, the establishment of or amendments to equity-based compensation plans for employees, a change of control of us and certain private placements. To this extent, our practice varies from the requirements of Nasdaq Rule 5635, which generally requires an issuer to obtain shareholder approval for the issuance of securities in connection with such events. Accordingly, you may not have the same protections afforded to shareholders of companies that are subject to these Nasdaq requirements.

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

We report under the Exchange Act as a non-U.S. company with foreign private issuer status. Because we qualify as a foreign private issuer under the Exchange Act, we are exempt from certain provisions of the Exchange Act that are applicable to U.S. domestic public companies, including (i) the sections of the Exchange Act regulating the solicitation of proxies, consents or authorizations in respect of a security registered under the Exchange Act, (ii) the sections of the Exchange Act requiring insiders to file public reports of their stock ownership and trading activities and liability for insiders who profit from trades made in a short period of time and (iii) the rules under the Exchange Act requiring the filing with the SEC of annual reports on Form 10-Q containing unaudited financial and other specified information, or current reports on Form 8-K, upon the occurrence of specified significant events. In addition, foreign private issuers are not required to file their annual report on Form 20-F until four months after the end of each fiscal year, while U.S. domestic issuers that are accelerated filers are required to file their annual report on Form 10-K within 75 days after the end of each fiscal year. Foreign private issuers are also exempt from the Regulation Fair Disclosure, aimed at preventing issuers from making selective disclosures of material information. As a result of the above, you may not have the same protections afforded to shareholders of companies that are not foreign private issuers.

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

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

The regulatory and compliance costs to us under U.S. securities laws as a U.S. domestic issuer may be significantly more than costs we incur as a foreign private issuer. If we are not a foreign private issuer, we will be required to file periodic reports and registration statements on U.S. domestic issuer forms with the SEC, which are more detailed and extensive in certain respects than the forms available to a foreign private issuer. We would be required under current SEC rules to prepare our financial statements in accordance with U.S. Generally Accepted Accounting Principles, or U.S. GAAP, rather than IFRS, as issued by IASB. Such conversion of our financial statements to U.S. GAAP would involve significant time and cost, and we would still be required to prepare financial statements in accordance with IFRS as required by Dutch law. In addition, we may lose our ability to rely upon exemptions from certain corporate governance requirements on United States stock exchanges that are available to foreign

private issuers such as the ones described above and exemptions from procedural requirements related to the solicitation of proxies.

We are eligible to be treated as an "emerging growth company," as defined in the JOBS Act, and we cannot be certain if the reduced disclosure requirements applicable to emerging growth companies will make our ordinary shares less attractive to investors.

We are an emerging growth company, as defined in the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including an exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting pursuant to the Sarbanes-Oxley Act; and to the extent that we no longer qualify as a foreign private issuer, (a) reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and (b) exemptions from the requirements of holding a nonbinding advisory vote on executive compensation, including golden parachute compensation. We cannot predict whether investors will find our ordinary shares less attractive if we rely on these exemptions. If some investors find our ordinary shares less attractive as a result, there may be a less active trading market for our ordinary shares and our share price may be reduced or more volatile.

We may take advantage of these provisions until such time that we are no longer an emerging growth company. We would cease to be an emerging growth company following the fifth anniversary of the date of the completion of this offering or earlier if we have more than $1.07 billion in annual revenues, are deemed to be a "large accelerated filer" under the rules of the SEC, or issue more than $1.0 billion of nonconvertible debt over a three-year period. We may also choose to take advantage of some but not all of these reduced burdens. For example, Section 107 of the JOBS Act provides that an emerging growth company can use the extended transition period provided in Section 7(a)(2)(B) of the Securities Act of 1933, as amended, or the Securities Act, for complying with new or revised accounting standards. Given that we currently report and expect to continue to report under IFRS, as issued by the IASB, we have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required by the IASB.

The rights of shareholders in companies subject to Dutch corporate law differ in material respects from the rights of shareholders of corporations incorporated in the United States.

Our corporate affairs are governed by our Articles of Association, our internal rules and policies and by Dutch law. The rights of shareholders and the responsibilities of members of our Board are in many ways different from the rights and obligations of shareholders and a board of directors in companies governed by the laws of United States jurisdictions. In particular, pursuant to Dutch law members of the Board are required to act in the interest of the company and the sustainable success of its business, with an aim to creating long-term value, taking into account the interests of its employees, clients, shareholders and other stakeholders of the company, 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 a shareholder.

Dutch corporate law and our Articles of Association contain or may contain provisions that may discourage, delay or prevent a takeover attempt, which could adversely affect the price of our ordinary shares.

Under Dutch law, various protective measures are possible and permissible within the boundaries set by Dutch law and Dutch case law. In this respect, our general meeting has authorized our Board for a period of five years after our conversion into a Dutch public company with limited liability (naamloze vennootschap), to grant a call option to an independent foundation under Dutch law (if and when incorporated), or protective foundation, to acquire preferred shares pursuant to a call option agreement that may be entered into between us and such protective foundation.

This call option, if and when granted, shall be continuous in nature and can be exercised repeatedly on multiple occasions. If the protective foundation, if and when incorporated, would exercise such call option, if and when granted, a number of preferred shares up to 100% of our issued share capital held by others than the protective foundation, minus one share, will be issued to the protective foundation. These preferred shares would then be issued to the protective foundation under the obligation to pay up 25% of their nominal value upon issuance. In order for the protective foundation to finance the issue price in relation to the preferred shares, the protective foundation may enter into a finance arrangement with a bank or other financial institution. As an alternative to securing this external financing, subject to applicable restrictions under Dutch law, the call option agreement, if and when entered into, will provide that the protective foundation may request us to provide, or cause our subsidiaries to provide, sufficient funding to the protective foundation to enable it to satisfy the payment obligation (or part thereof) in cash and/or to charge an amount equal to the payment obligation (or part thereof) against our profits and/or reserves in satisfaction of such payment obligation. The articles of association of the protective foundation, if and when incorporated, will provide that it will promote and protect the interests of the Company, the business connected with the Company and the Company's stakeholders from time to time, and repressing possible influences which could threaten the strategy, continuity, independence and/or identity of the company or the business connected with it, to such an extent that this could be considered to be damaging to the aforementioned interests. These influences may include a third party acquiring a significant percentage of our ordinary shares, the announcement of an unsolicited public offer for our ordinary shares, shareholder activism, other concentration of control over our ordinary shares or any other form of undue pressure on us to alter our strategic policies. The protective foundation, if and when incorporated, shall be structured to operate independently of us.

The voting rights of our shares are based on nominal value and, as we expect our ordinary shares to trade substantially in excess of their nominal value, preferred shares issued at 25% of their nominal value can carry significant voting power for a substantially reduced price compared to the price of our ordinary shares and thus can be used as a defensive measure. These preferred shares, if and when issued, will have both a liquidation and dividend preference over our ordinary shares and will accrue a cash preferred dividend at a fixed rate calculated over the amount paid-up on those preferred shares pro rata tempore for the period during which they were outstanding. The protective foundation would be expected to require us to cancel its preferred shares, if and when issued to the protective foundation, once the perceived threat to the company and its stakeholders has been removed or sufficiently mitigated or neutralized. However, subject to the same limitations described above, the protective foundation would, in that case, continue to have the right to exercise the call option in the future in response to a new threat to the interests of us, our business and our stakeholders from time to time.

In addition, we have adopted several provisions that may have the effect of making a takeover of our Company more difficult or less attractive, including:

- our directors being appointed on the basis of a binding nomination by our Board, which can only be overruled by the general meeting by a resolution adopted by at least a two-thirds

majority of the votes cast, provided such majority represents more than half of our issued share capital (in which case the Board shall make a new nomination);

- a provision that our directors may only be removed by the general meeting by a two-thirds majority of the votes cast representing more than half of our issued share capital if such removal is not proposed by our Board;
- a provision which allows the most recent (former) chairman of our Board or our most recent (former) chief executive officer to be charged with our management if all of our directors are absent or incapacitated; and
- requirements that certain matters, including an amendment of our Articles of Association, may only be brought to our shareholders for a vote upon a proposal by our Board.

In addition, Dutch law allows for staggered multi-year terms of our directors, as a result of which only part of our directors may be subject to appointment or re-appointment in any one year.

Dutch cooling-off period in face of shareholder activism or hostile take-over.

As of May 1, 2021, a statutory cooling-off period of up to 250 days was introduced, during which, if invoked by the Board, the general meeting of shareholders would not be able to dismiss, suspend or appoint members of the Board (or amend the provisions in the Articles of Association dealing with those matters) unless those matters would be proposed by the Board. This cooling-off period could be invoked by the board of directors in case:

a. shareholders, using either their shareholder proposal right or their right to request a general meeting of shareholders, propose an agenda item for the general meeting to dismiss, suspend or appoint a director (or to amend any provision in the Articles of Association dealing with those matters); or
b. a public offer for the Company is made or announced without our support, provided, in each case, that the Board believes that such proposal or offer materially conflicts with the interests of the Company and its business.

The cooling-off period, if invoked, ends at occurrence of the earliest of the following events:

a. the expiration of 250 days from:
    i. in case of shareholders using their shareholder proposal right, the day after the deadline for making such proposal expired;
    ii. in case of shareholders using their right to request a general meeting of shareholders, the day when they obtain court authorization to do so; or
    iii. in case of a hostile offer being made, the first following day;
b. the day after the hostile offer having been declared unconditional; or
c. the Board voluntarily terminating the cooling-off period.

In addition, shareholders representing at least 3% of our issued share capital may request the Dutch Enterprise Chamber of the Amsterdam Court of Appeals for early termination of the cooling-off period. The Enterprise Chamber must rule in favour of the request if the shareholders can demonstrate that:

a. the Board, in light of the circumstances at hand when the cooling-off period was invoked, could not reasonably have come to the conclusion that the relevant shareholder proposal or hostile offer constituted a material conflict with the interests of the Company and its business;
b. the Board cannot reasonably believe that a continuation of the cooling-off period would contribute to careful policy-making;
c. if other defensive measures have been activated during the cooling-off period and not terminated or suspended at the relevant shareholders' request within a reasonable period following the request (i.e., no 'stacking' of defensive measures).

During the cooling-off period, if invoked, the Board must gather all relevant information necessary for a careful decision-making process. In this context, the Board must at least consult with shareholders representing at least 3% of our issued share capital at the time the cooling-off period was invoked and with the Dutch works council (in case such works council is established). Formal statements expressed by these stakeholders during such consultations must be published on our website to the extent these stakeholders have approved that publication.

Ultimately one week following the last day of the cooling-off period, the board of directors must publish a report in respect of its policy and conduct of affairs during the cooling-off period on our website. This report must remain available for inspection by shareholders and others with meeting rights under Dutch law at our office and must be tabled for discussion at the next general meeting.

Shareholders 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 our 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. Our Board is authorized for a period of five years after our conversion into a Dutch public company with limited liability (naamloze vennootschap) to issue shares or grant rights to subscribe for shares up to our authorized share capital from time to time and to limit or exclude preemptive rights in connection therewith. This could cause existing shareholders to experience substantial dilution of their interest in us.

U.S. investors may have difficulty enforcing civil liabilities against our company and directors and senior management.

We are incorporated under the laws of the Netherlands and have our statutory seat (statutaire zetel) in Leiden, the Netherlands. Some of our assets are located outside the United States and most members of the Board and Senior Management reside outside of the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce against them or us the U.S. courts' judgments predicated upon the civil liability provisions of the federal securities laws of the United States.

Foreign courts may refuse to hear a United States securities law claim because foreign courts may not be the most appropriate forums in which to bring such a claim. Even if a foreign court agrees to hear a claim, it may determine that the law of the jurisdiction in which the foreign court resides, and not U.S. law, is applicable to the claim.

Further, if U.S. law is found to be applicable, the content of applicable U.S. law must be proved as a fact, which can be a time-consuming and costly process, and certain matters of procedure would

still be governed by the law of the jurisdiction in which the foreign court resides.

There is currently no treaty between the United States and the Netherlands for the mutual recognition and enforcement of judgments (other than arbitration awards) in civil and commercial matters. Therefore, a final judgment for the payment of money rendered by any federal or state court in the United States based on civil liability, whether or not predicated solely upon the U.S. federal securities laws, would not be enforceable in the Netherlands unless the underlying claim is relitigated before a Dutch court of competent jurisdiction. Under current practice, however, a Dutch court will generally, subject to compliance with certain procedural requirements, grant the same judgment without a review of the merits of the underlying claim if such judgment (i) is a final judgment and has been rendered by a court, which has established its jurisdiction vis-à-vis the relevant Dutch companies or Dutch company, as the case may be, on the basis of internationally accepted grounds of jurisdiction, (ii) has not been rendered in violation of principles of proper procedure (behoorlijke rechtspleging), (iii) is not contrary to the public policy of the Netherlands, and (iv) is not incompatible with (a) a prior judgment of a Dutch court rendered in a dispute between the same parties or (b) a prior judgment of a foreign court rendered in a dispute between the same parties, concerning the same subject matter and based on the same cause of action, provided that such prior judgment is capable of being recognized in the Netherlands and except to the extent that the foreign judgment contravenes Dutch public policy (openbare orde). Dutch courts may deny the recognition and enforcement of punitive damages or other awards. Moreover, a Dutch court may reduce the amount of damages granted by a U.S. court and recognize damages only to the extent that they are necessary to compensate actual losses or damages. Enforcement and recognition of judgments of U.S. courts in the Netherlands are solely governed by the provisions of the Dutch Code of Civil Procedure (Wetboek van Burgerlijke Rechtsvordering).

Additionally, our Articles of Association provide that the U.S. federal district courts shall be the sole and exclusive forum for any claim asserting a cause of action arising under the Securities Act. This choice of forum provision may limit a shareholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees and may increase the costs associated with such lawsuits, which may discourage such lawsuits against us and our directors, officers and employees.

Based on the foregoing, there can be no assurance that U.S. investors will be able to enforce any judgments obtained against us, members of the Board and our Senior Management, who are residents of or possessing assets in the Netherlands or other countries other than the United States, in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

We may be a passive foreign investment company, or "PFIC," which could result in adverse U.S. federal income tax consequences to U.S. investors.

Under the United States Internal Revenue Code of 1986, as amended, or the Code, we will be a PFIC for any taxable year in which, after the application of certain look-through rules with respect to subsidiaries, either (i) 75% or more of our gross income consists of "passive income," or (ii) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, "passive income." Passive income generally includes dividends, interest, certain non-active rents and royalties, and capital gains. We do not believe we were a PFIC in 2020 and we do not expect to be a PFIC for our current taxable year or in the foreseeable future. In addition, we may, directly or indirectly, hold equity interests in other PFICs. Whether we or any of our subsidiaries will be a PFIC in 2021 or any future year is a factual determination that must be made annually at the close of each taxable year, and, thus, is subject to significant uncertainty. Because a determination of whether a

company is a PFIC must be made annually after the end of each taxable year and will depend on the composition of our income and assets and the market value of our assets from time to time, we cannot assure you that we will not be a PFIC for the current or any future taxable year. Accordingly, there can be no assurance that we will not be a PFIC in 2021 or any future taxable year.

If we are a PFIC for any taxable year during which a U.S. Holder (as defined in "Material United States and Dutch Income Tax Considerations—Material U.S. Federal Income Tax Considerations to U.S. Holders") holds our ordinary shares, we generally would continue to be treated as a PFIC with respect to that U.S. investor for all succeeding years during which the U.S. Holder holds our ordinary shares even if we ceased to meet the threshold requirements for PFIC status, unless certain exceptions apply. Such a U.S. Holder may be subject to adverse U.S. federal income tax consequences, including (i) the treatment of all or a portion of any gain on disposition as ordinary income, (ii) the application of a deferred interest charge on such gain and the receipt of certain dividends and (iii) compliance with certain reporting requirements. There is no assurance that we will provide information that will enable investors to make a qualified electing fund election, also known as a QEF Election, which could mitigate the adverse U.S. federal income tax consequences should we be classified as a PFIC.

General Risk Factors

Our internal computer systems, or those used by our clinical investigators, contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our contractors and consultants are vulnerable to damage from cyber-attacks or intrusions, including by computer hackers, foreign governments, foreign companies or competitors, or may be breached by employee error, malfeasance or other disruption. A breakdown, invasion, corruption, destruction or interruption of critical information technology systems could negatively impact operations. If our systems are damaged, fail to function properly or otherwise become unavailable, we may incur substantial costs to repair or replace them, and we may experience loss of critical data and interruptions or delays in our ability to perform critical functions, which could adversely affect our business, financial condition or results of operations. For example, the loss of clinical trial data from clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could be subject to significant fines, penalties or other liabilities and the development and commercialization of our product candidates could be delayed, which could have a material adverse effect on our business, results of operations, financial condition and prospects. Some of the federal, state and foreign government requirements also include obligations of companies to notify regulators and/or individuals of security breaches involving personally identifiable information, which could result from breaches experienced by us or by our vendors, contractors, or organizations with which we have formed strategic relationships. Even though we may have contractual protections with such vendors, contractors, or other organizations, notifications and follow-up actions related to a security breach could impact our reputation and cause us to incur significant costs. Any failure to prevent or mitigate security breaches or improper access to, use, disclosure or other misappropriation of our data or consumers' personal data could result in significant liability under state (e.g., state breach notification and privacy laws), federal (e.g., the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH Act)) and international laws

(e.g., the GDPR). For example, a breach impacting personal data which is subject to the GDPR could result in fines of up to 20 million Euros or up to 4% of the total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims for financial or non-financial loss by affected individuals. To the extent that any disruption or security breach resulted in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed. For example, the loss of or damage to clinical trial data, such as from completed or ongoing clinical trials, for any of our product candidates would likely result in delays in our marketing approval efforts and significantly increased costs in an effort to recover or reproduce the data.

We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

We may consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of intellectual property, products or technologies. Any future transactions could increase our near and long-term expenditures, result in potentially dilutive issuances of our equity securities, including our ordinary shares, or the incurrence of debt, contingent liabilities, amortization expenses or acquired in process research and development expenses, any of which could affect our financial condition, liquidity and results of operations. Additional potential transactions that we may consider in the future include a variety of business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. These transactions may never be successful and may require significant time and attention of management. In addition, the integration of any business that we may acquire in the future may disrupt our existing business and may be a complex, risky and costly endeavor for which we may never realize the anticipated benefits. Accordingly, although there can be no assurance that we will undertake or successfully complete any transactions of the nature described above, any transactions that we do complete could have a material adverse effect on our business, results of operations, financial condition and prospects.

The trading price of our ordinary shares has been and may in the future be highly volatile, which could result in substantial losses for holders of our ordinary shares.

Our share price is likely to be highly volatile. In addition, because of our relatively small public float our ordinary shares may be less liquid than the ordinary shares of companies with broader public ownership and trading of a relatively small volume of our ordinary shares may have a greater impact on the market price for our ordinary shares than would be the case if our public float were larger. The market price of our ordinary shares may fluctuate significantly in response to numerous factors, many of which are beyond our control, including, but not limited to:

- results and timing of clinical trials of our and our competitors' product candidates;
- failure of any of our product candidates, if approved, to achieve commercial success;
- competition from existing products or new products that may emerge;
- issues in manufacturing our product candidates or future approved products;
- public concern relating to the commercial value or safety of any of our product candidates;
- disputes or other developments related to proprietary rights, including patents, litigation matters, and our ability to obtain intellectual property protection for our technologies;
- failure to adequately protect our trade secrets;

- additions and departures of key personnel;
- our inability to raise additional capital or the terms on which we raise it;
- period-to-period fluctuations in our financial condition and results of operations, including the timing of receipt of any milestone or other payments under commercialization or licensing agreements;
- public health crises, illnesses, epidemics or pandemics, such as the COVID-19 pandemic;
- changes in market conditions for biopharmaceutical stocks;
- changes in general market and economic conditions; and
- other risk factors discussed in this section.

In addition, the stock market in general has experienced substantial price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of particular companies affected. These broad market and industry factors may materially harm the market price of our ordinary shares, regardless of our operating performance. As we operate in a single industry, we are especially vulnerable to these factors to the extent that they affect our industry or our product candidates, or to a lesser extent our markets. In the past, securities class action litigation has often been initiated against companies and their management following periods of volatility in their stock price. This type of litigation could result in substantial costs and divert our management's attention and resources, and could also require us to make substantial payments to satisfy judgments or to settle litigation.

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

The trading market for our ordinary shares depends in part on the research and reports that securities or industry analysts publish about us or our business. If no or few securities or industry analysts cover us, the trading price for our ordinary shares would likely be negatively impacted. If one or more of the analysts who covers us downgrades our ordinary shares or publishes incorrect or unfavorable research about our business, the price of our ordinary shares would likely decline. If one or more of these analysts ceases coverage of us or fails to publish reports on us regularly, or downgrades our ordinary shares, demand for our ordinary shares could decrease, which could cause the price of our ordinary shares or trading volume to decline.

We will incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an "emerging growth company," we will incur significant legal, accounting and other expenses. The Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of Nasdaq and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We expect that we will need to hire additional accounting, finance and other personnel in connection with our becoming, and our efforts to comply with the requirements of being, a public company and our management and other personnel will need to devote a substantial amount of time towards maintaining compliance with these requirements. These requirements will increase our legal and financial compliance costs and will make some activities more time- consuming and costly. For example, we expect that the rules and regulations applicable to us as a public company may make it

more difficult and more expensive for us to obtain director and officer liability insurance, which could make it more difficult for us to attract and retain qualified members of our Board. We are currently evaluating these rules and regulations and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. 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.

If our estimates or judgments relating to our critical accounting policies are based on assumptions that change or prove to be incorrect, our operating results could fall below the expectations of securities analysts and investors, resulting in a decline in the market price of our ordinary shares.

The preparation of financial statements in conformity with IFRS requires management to make estimates and assumptions that affect the amounts reported in our financial statements and accompanying notes. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets, liabilities, equity, revenue and expenses that are not readily apparent from other sources. It is possible that interpretation, industry practice and guidance may evolve over time. If our assumptions change or if actual circumstances differ from our assumptions, our operating results may be adversely affected and could fall below the expectations of securities analysts and investors, resulting in a decline in the market price of our ordinary shares.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud. We designed our disclosure controls and procedures to provide reasonable assurance that information we must disclose in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

4 CONTROLS AND PROCEDURES

4.1 Risk management and control systems

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements in accordance with IFRS. As a result of becoming a public company, we will be required, pursuant to Section 404 of the Sarbanes-Oxley Act to furnish a report by our management on, among other things,

the effectiveness of our internal control over financial reporting in our annual report for the year ended December 31,2021. This assessment will need to include disclosures of any material weaknesses identified by our management in our internal control over financial reporting. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting such that there is a reasonable possibility that a material misstatement of a company's annual or interim financial statements will not be detected or prevented on a timely basis.

In connection with the preparation of our financial statements as of and for the years ended December 31, 2018, 2019 and 2020 we identified material weaknesses in the design of our internal control over financial reporting across the principles for each component of the COSO framework at the entity level (i.e. control environment, risk assessment, monitoring, information & communication and control activities) and accordingly, across our business and IT processes. The material weaknesses that we identified related to:

- the lack of consistent and documented risk assessment procedures and control activities related to our financial reporting, among which a sufficient level of (management) review and approval, manual processes, roles and responsibilities, and adequate application and controls over information technology; and

- our failure to maintain a sufficient complement of personnel commensurate with our accounting and reporting requirements as we continue to grow as a company, and ability to: (i) design and maintain formal accounting policies, procedures and controls over the fair presentation of our financial statements; (ii) analyze, record and disclose complex accounting matters timely and accurately, including share-based compensation arrangements and other non-routine transactions; and (iii) design and maintain controls over the preparation and review of journal entries and financial statements, including maintaining appropriate segregation of duties.

Although several oversight and control activities are performed, not all activities are formalized and documented properly. In addition, where control activities are dependent on information used in a control, we do not perform or document controls to determine the completeness and accuracy of such information. We also did not have controls in place to monitor control activities and identify control deficiencies.

To address these material weaknesses, we will need to add personnel and continue to develop and implement new financial processes. We intend to take steps to remediate the material weaknesses described above through hiring additional qualified accounting and financial reporting personnel, and further evolving our accounting processes and policies. We will not be able to fully remediate these material weaknesses until these steps have been completed and have been operating effectively for a sufficient period of time. We cannot provide assurances that we will be able to successfully remediate these material weaknesses or that other material weakness will not be discovered in the future.

4.2 In control statement

As at 31 December 2020, the Company was not bound by the DCGC, so the Board did not

perform a formal self-evaluation during the financial year to which this report pertains.

5 CORPORATE GOVERNANCE

5.1 Dutch Corporate Governance Code

The Company acknowledges the importance of good corporate governance. With effect from the consummation of the IPO, the Dutch Corporate Governance Code (the "**DCGC**") became applicable to the Company. However, for the fiscal year ended 31 December 2020, the DCGC did not yet apply to the Company. Consequently, the Company does not consider itself to have been bound by the DCGC during the fiscal year ended 31 December 2020 nor to have deviated from any of the principles and best practice provisions of the DCGC in such fiscal year. Similarly, the Company does not consider the disclosure recommendations promulgated by the DCGC with respect to the contents of a listed company's board report to be relevant with respect to this report, because this report pertains to a fiscal year during which the DCGC did not apply to the Company. Nevertheless, these disclosure recommendations have been addressed in this report on a voluntary basis to the extent we believe they are appropriate.

Without prejudice to what is stated above, the Company has reviewed the DCGC and supports the principles and best practice provisions thereof. As of the date of publication of this report, the Company is not aware of (actual or intended) material deviations from the DCGC during the fiscal year 2021 other than the ones listed below (but cannot exclude the possibility of deviating from one or more provisions of the DCGC after the date of this report):

- Under the Company's articles of association, directors are be appointed on the basis of a binding nomination prepared by the Board. This means that the nominee will be appointed to the Board, unless the general meeting of the Company (the "**General Meeting**") overrules the binding nature of the nomination (in which case a new nomination will be prepared for a subsequent General Meeting). The Company's articles of association provide that the General Meeting can only pass such resolution by at least a two-thirds majority of the votes cast, provided such majority represents more than half of the issued share capital. However, the DCGC recommends that the General Meeting should be capable of passing such a resolution by a simple majority of votes cast, representing no more than one-third of the issued share capital.

- Under the Company's articles of association, directors can only be dismissed by the General Meeting by simple majority of votes cast, provided that the Board proposes the dismissal. In other cases, the General Meeting can only pass such resolution by a two-thirds majority representing more than half of the issued share capital. The DCGC recommends that the General Meeting can pass a resolution to dismiss a director by simple majority, representing no more than one-third of the issued share capital.

- The DCGC recommends against providing equity awards as part of the compensation of a non-executive director. However, consistent with U.S. market practice, we have granted awards to our non-executive directors.

- The Pharvaris N.V. 2021 Equity Incentive Plan allows us to set the terms and conditions of equity awards granted thereunder. Under the Plan, we may grant ordinary shares that are not subject to a lock-up period of at least five years after the date of grant, and we may grant options without restricting the exercisability of those options during the first three years after the date of grant. In those cases, this would cause additional deviations from the DCGC.
  The text of the DCGC can be accessed at http://www.mccg.nl.

5.2 Code of business conduct and ethics and other corporate governance practices

As at 31 December 2020, the Company did not voluntarily apply formal codes of conduct or corporate governance practices. However, in connection with the IPO, the Company has adopted a code of business conduct and ethics which can be accessed at https://ir.pharvaris.com/corporate-governance/governance-documents. The Company does not voluntarily apply any other formal codes of conduct or corporate governance practices.

5.3 Risk management and control systems and internal audit function

See chapter 4.1 of this report for an overview of the main characteristics of the Company's risk management and control systems relating to the process of financial reporting by the Company and the Company's group companies whose financial information is included in the consolidated financial statements.
The Company has not established an internal audit function.

5.4 General Meeting

5.4.1 Functioning of the General Meeting

Annually, at least one General Meeting must be held. This annual General Meeting must be held within six months after the end of the Company's fiscal year. A General Meeting must also be held within three months after the Board has decided that it is likely that the Company's equity has decreased to or below 50% of its paid up and called up share capital. In addition, without prejudice to the relevant best practice provisions of the DCGC with respect to invoking a 'response period', a General Meeting must be held when requested by one or more shareholders and/or others with meeting rights under Dutch law collectively representing at least 10% of the Company's issued share capital, provided that certain criteria are met. Any additional General Meeting shall be convened whenever the Board would so decide. Each General Meeting must be held in Amsterdam, Arnhem, Assen, The Hague, Haarlem, 's-Hertogenbosch, Groningen, Leeuwarden, Lelystad, Leiden, Maastricht, Middelburg, Rotterdam, Schiphol (Haarlemmermeer), Utrecht or Zwolle.

For purposes of determining who have voting rights and/or meeting rights under Dutch law at a General Meeting, the Board may set a record date. The record date, if set, shall be the 28th day prior to that of the General Meeting. Those who have voting rights and/or meeting rights under Dutch law on the record date and are recorded as such in one or more registers designated by the Board shall be considered to have those rights at the General Meeting, irrespective of any changes in the composition of the shareholder base between the record date and the date of the General Meeting. The Company's articles

of association require shareholders and others with meeting rights under Dutch law to notify the Company of their identity and their intention to attend the General Meeting. This notice must be received by the Company ultimately on the seventh day prior to the General Meeting, unless indicated otherwise when such General Meeting is convened.

5.4.2 Powers of the General Meeting

All powers that do not vest in the Board pursuant to applicable law, the Company's articles of association or otherwise, vest in the Company's general meeting. The main powers of the General Meeting include, subject in each case to the applicable provisions in the Company's articles of association:

a. the appointment, suspension and dismissal of Directors;

b. the approval of certain resolutions of the Board concerning a material change to the identity or the character of the Company or its business;

c. the reduction of the Company's issued share capital through a decrease of the nominal value, or cancellation, of shares in its capital;

d. the adoption of the Company's statutory annual accounts;

e. the appointment of the Dutch independent auditor to examine the Company's statutory annual accounts;

f. amendments to the Company's articles of association;

g. approving a merger or demerger by the Company, without prejudice to the authority of the Board to resolve on certain types of mergers and demergers if certain requirements are met; and

h. the dissolution of the Company.

In addition, the General Meeting has the right, and the Board must provide, any information reasonably requested by the General Meeting, unless this would be contrary to an overriding interest of the Company.

5.4.3 Shareholder rights

Each share in the Company's capital carries one vote. Shareholders, irrespective of whether or not they have voting rights, have meeting rights under Dutch law (including the right to attend and address the General Meeting, subject to the concept of a record date as described in chapter 5.4.1). Furthermore, each share in the Company's capital carries an entitlement to dividends and other distributions as set forth in the Company's articles of association. Pursuant to the Company's articles of association, any such dividend or other distribution shall be payable on such date as determined by the Board and the

Board may also set a record date for determining who are entitled to receive any such dividend or other distribution (irrespective of subsequent changes in the shareholder base). The record date for dividends and other distributions shall not be earlier than the date on which the dividend or other distribution is announced. In addition, shareholders have those rights awarded to them by applicable law.

5.5 Board

Our executive director is charged primarily with the Company's day-to-day business and operations and the implementation of the Company's strategy. Our non-executive directors are charged primarily with the supervision of the performance of the duties of the Board. Each director is charged with all tasks and duties of the Board that are not delegated to one or more other specific directors by virtue of Dutch law, the Company's articles of association or any arrangement catered for therein (e.g., the internal rules of the Board). In performing their duties, our directors shall be guided by the interests of the Company and of the business connected with it.

Our Board has developed a view on long-term value creation by the Company and has formulated a strategy consistent with that view. The non-executive directors have been actively engaged at an early stage in formulating the Company's strategy and supervise the manner in which the strategy is implemented.

As at December 31, 2020, the Board was composed as follows, which are all current directors on the Board as of the date of this report (except for Michael Rome, who resigned on January 1, 2021 and Richard Gaster, who resigned with effect from May 1, 2021):

Name and age	Gender	Nationality	Date of initial appointment	Expiration of current term of office**
Berndt Modig (62) *	M	Swedish and American	September 30, 2015	At the end of the AGM to be held in 2024
Rémi Droller (45) **	M	French	April 15, 2016	At the end of the AGM to be held in 2023
Hans Schikan (62) **	M	Dutch	August 28, 2019	At the end of the AGM to be held in 2024
Martijn Kleijwegt (66) **	M	Dutch	April 15, 2016	At the end of the AGM to be held in 2023
Michael Rome***	M	American	July 2, 2020	N/A
Richard Gaster (36) ****	M	American	August 1, 2019	At the end of the AGM to be held in 2022

On January 1, 2021, the following two individuals were appointed on the Board (that constitute, together with the individuals listed above (other than Michael Rome and Richard Gaster), the entire Board as of the date of this report):

Name and age	Gender	Nationality	Date of initial appointment	Expiration of current term of office**
David Meeker (66) **	M	American	January 1, 2021	At the end of the AGM to be held in 2025
Robert Glassman (60) **	M	American	January 1, 2021	At the end of the AGM to be held in 2025

* Executive director.
** Non-executive director.
*** Non-executive director, who resigned on from January 1, 2021.
**** Non-executive director, who resigned on from May 1, 2021.

Board

Berndt Modig

Mr. Modig is a co-founder of the Company and has served as Chief Executive Officer since its inception. Mr. Modig is also a director of the Company. Prior to co-founding the Company, Mr. Modig served as Chief Financial Officer of Prosensa Holding N.V., a biopharmaceutical company focusing on novel RNA modulating treatments for rare diseases like Duchenne muscular dystrophy, from March 2010 through its IPO on the NASDAQ in 2013 until its acquisition by BioMarin Pharmaceutical Inc. in January 2015.

From October 2003 to November 2008, Mr. Modig was Chief Financial Officer at Jerini AG through its IPO on the Frankfurt exchange in 2005 and sale to Shire plc in 2008. Jerini developed and launched icatibant for the treatment of HAE, now currently marketed by Shire plc under the FIRAZYR brand name. Before Jerini AG, Mr. Modig served as Chief Financial Officer at Surplex AG from 2001 to 2003 and as Finance Director Europe of U.S.-based Hayward Industrial Products Inc. from 1999 to 2001. In previous positions, Mr. Modig was a Partner in the Brussels-based private equity firm Agra Industria from 1994 to 1999 and a Senior Manager in the Financial Services Industry Group of Price Waterhouse LLP in New York from 1991 to 1994.

Mr. Modig also serves as a director, chair of the compensation committee and member of the audit committee of Sio Gene Therapies Inc., and as a member of the supervisory board and chair of the audit committee of Centogene N.V., all publicly held pharmaceutical companies. Mr. Modig received a bachelor's degree in business administration, economics and German from the University of Lund, Sweden, and an MBA from INSEAD, Fontainebleau, France. Mr. Modig is a certified public accountant (inactive). We believe that Mr. Modig is qualified to serve on our Board because of his extensive international experience in finance and operations, private equity and mergers and acquisitions, and his service on the boards of directors of other biopharmaceutical companies.

Rémi Droller

Mr. Droller has been a director since April 2016. Mr. Droller has been working as Managing Partner with Kurma Partners since 2010 and is in charge of investments in AM Pharma, Orphazyme, Oxthera (Sweden), ImCheck (France), Stat Dx, Zealand Pharma, Vico Therapeutics, Flamingo Therapeutics and Dynacure. Mr. Droller started at CDC Innovation (now bpi France) from 2000 to 2003, later joining AGF Private Equity (now Idinvest Partners) where he developed the investment activity in the life sciences and made investments such as Novagali Pharma, Prosensa Holding N.V., Vivacta, IntegraGen, and Onxeo.

Mr. Droller holds a Master in Molecular Biology (Paris VI) and Master in Finance and Innovation Management (Masternova – AgroPariTech). We believe that Mr. Droller is qualified to serve on our Board because of his extensive experience as a venture capital investor and his service on the boards of directors of other biopharmaceutical companies.

Hans Schikan, PharmD

Mr. Schikan is a co-founder of the Company and has been a director since August 28, 2019. Mr. Schikan is the former CEO of Prosensa Holding N.V., a biopharmaceutical company focusing on novel RNA modulating treatments for rare diseases including Duchenne muscular dystrophy.

Mr. Schikan was previously at Genzyme, most recently serving as VP for Global Marketing and Strategic Development of Genzyme's product portfolio for rare genetic diseases. He is currently Chairman of the Board of Complix, InteRNA and Microbiotica, Board Member of Vicore Pharma and VectivBio.

Mr. Schikan is also member of the Top Team of the Dutch Top Sector Life Sciences & Health. Previously, he served on the boards of Sobi, Hansa Biopharma, Asceneuron, Wilson Therapeutics (acquired by Alexion) and Therachon (acquired by Pfizer). Mr. Schikan has a Pharm.D. degree from Utrecht University. We believe that Mr. Schikan is qualified to serve on our Board because of his extensive senior managerial experience in the pharmaceutical and biotechnology industries, his role as CEO of Prosensa Holding N.V. and his service on the boards of directors of other biopharmaceutical companies.

Martijn Kleijwegt

Mr. Kleijwegt has been a director since April 2016. Mr. Kleijwegt founded LSP in 1998 and is currently a Managing Partner and co-owner of LSP. Mr. Kleijwegt brings over 30 years of hands-on finance and investment experience to the Company. We believe that Mr. Kleijwegt is qualified to serve on our Board because of his experience in the biopharmaceutical industry as a venture capital investor, a founder of Life Sciences Partners and a member of the boards of directors of other biopharmaceutical companies.

David Meeker, M.D.

Dr. Meeker has been a director since January 2021. Dr. Meeker is the Chairman of the Board, President and Chief Executive Officer of Rhythm Pharmaceuticals, Inc. Prior to joining Rhythm

Pharmaceuticals, Dr. Meeker served as President and Chief Executive Officer of KSQ Therapeutics, Inc. from 2017 to 2020. Prior to joining KSQ, Dr. Meeker worked at Sanofi Genzyme from 2011 to 2017, in a variety of roles, including as President and Chief Executive Officer of Genzyme, a Sanofi Company, as a member of Sanofi's Executive Committee, and as Executive Vice President and Head of Sanofi Genzyme, Sanofi's specialty care unit with responsibility for rare diseases, multiple sclerosis, oncology and immunology franchises. Prior to joining Genzyme, Dr. Meeker was Director of the Pulmonary Critical Care Fellowship at the Cleveland Clinic. Dr. Meeker has served as Chair of Trevi Therapeutics since 2017. He also served as a Director of MyoKardia, Inc. until its acquisition by Bristol Myers Squibb. Dr. Meeker holds a medical degree from the University of Vermont Medical School and completed the Advanced Management Program at Harvard Business School in 2000. We believe that Dr. Meeker is qualified to serve on our Board because of his extensive experience in the healthcare industry and as a member of the board of directors of other biopharmaceutical companies.

Robert Glassman, M.D.

Dr. Glassman has been a director since January 2021. Dr. Glassman is currently the Public Equity Venture Partner at OrbiMed Advisors. Previously, Dr. Glassman had been working as a senior investment banker for 17 years, most recently serving as Vice Chairman at Credit Suisse Securities since 2015. Prior to joining Credit Suisse Securities, Dr. Glassman served as a Managing Director at Bank of America Merrill Lynch between 2010-2015. From 2009-2010, Dr. Glassman served as a private equity partner at OrbiMed Advisors. Earlier in his career, Dr. Glassman was with Merrill Lynch Global Private Equity where he oversaw a very successful healthcare portfolio and at McKinsey & Co. where he consulted for a wide range of clients within their Pharmaceutical and Medical Products practice.

Dr. Glassman was a board certified hematologist-oncologist who remains on the faculty of Weil Cornell as a Clinical Assistant Professor of Medicine. He has co-authored numerous articles in peer-reviewed journals and spoken widely in industry and academic forums on clinical development, reimbursement, and data interpretation. Dr. Glassman received his AB from Harvard College magna cum laude and an MD from Harvard Medical School. He completed his residency in internal medicine at the Hospital of the University of Pennsylvania, and his fellowship in hematology and oncology at Weill Cornell. He also spent several years as a basic science investigator at Rockefeller University in the laboratory of Hidesaburo Hanafusa, where he received Howard Hughes Medical Institute and American Cancer Society awards. We believe that Dr. Glassman is qualified to serve on our Board because of his extensive experience as an investment banker and in the healthcare industry.

5.6 Committees

During 2020, the Company had a compensation committee ("**Compensation Committee**") in place. As at December 31, 2020, the Compensation Committee composed of Hans Schikan (as Chair), Martijn Kleijwegt and Michael Rome. The responsibilities of such Compensation Committee include, among others to oversee the Company's compensation policies, plans and programs, and to review and recommend to the Board the compensation to be paid to the Company's executive officers, as well as to review and discuss with management the Company's disclosures that may be contained in any information statements or other disclosures as required by applicable laws and to prepare and review the Compensation Committee report on executive compensation, if applicable.

During the fiscal year to which this report relates, the Compensation Committee met two times in order to carry out its responsibilities. The main items discussed at those meetings included the terms and conditions of our executive compensation and the long-term incentive grants to our staff.

In connection with the IPO during 2021, the composition and the charter of the Compensation Committee were amended to, among other things, comply with the relevant provisions applicable to the Company's listed environment and Nasdaq listing rules.

5.7 Evaluation

As at 31 December 2020, the Company was not bound by the DCGC, so the Board did not perform a formal self-evaluation during the financial year to which this report pertains.

5.8 Diversity

As at 31 December 2020, the Company was not bound by the DCGC, so the Board did not have in place a diversity policy during the financial year to which this report pertains. However, in connection with the IPO, the Company has adopted a diversity policy with respect to the composition of the Board. The Company is committed to supporting, valuing and leveraging the value of diversity. However, the importance of diversity, in and of itself, should not set aside the overriding principle that someone should be recommended, nominated and appointed for being "the right person for the job". Although the Company has not set specific targets with respect to particular elements of diversity, the Company believes that it is important for the Board to represent a diverse composite mix of personal backgrounds, experiences, qualifications, knowledge, abilities and viewpoints. The Company seeks to combine the skills and experience of long-standing members of the Board with the fresh perspectives, insights, skills and experiences of new members. To further increase the range of viewpoints, perspectives, talents and experience within the Board, the Company strives for a mix of ages in the composition of those bodies, but also does not set a specific target in this respect. The Company recognises and welcomes the value of diversity with respect to age, gender, race, ethnicity, nationality, sexual orientation and other important cultural differences. The Company is committed to seeking broad diversity in the composition of the Board and will consider these attributes when evaluating new candidates in the best interests of the Company and its stakeholders. In terms of experience and expertise, the Company intends for the Board to be composed of individuals who are knowledgeable in one or more specific areas detailed in the Company's diversity policy.

The Company believes that the composition of the Board is such, that the Company's diversity objectives, as outlined above, have been achieved.

5.9 Corporate values and code of business conduct and ethics

Following the completion of the IPO, we adopted a code of business conduct and ethics which covers a broad range of matters including the handling of conflicts of interest and other compliance matters such as insider trading, record keeping, workplace health and safety, fair-dealing, discrimination and harassment. We believe our code of business conduct and ethics is effective.

6 COMPENSATION

6.1 Compensation policy

As at 31 December 2020, the Company did not have a compensation policy, because the Company was not subject to a mandatory requirement or best practice provision to establish such a policy. However, in connection with the IPO, the General Meeting, in accordance with Section 2:135(1) DCC adopted a compensation policy (the "**Compensation Policy**"), which is designed to contribute to the Company's strategy, long-term interests and sustainability by:

a. attracting, retaining and motivating highly skilled individuals with the qualities, capabilities, profile and experience needed to support and promote the growth and sustainable success of the Company and its business;

b. driving strong business performance, promoting accountability and incentivising the achievement of short and long-term performance targets with the objective of furthering long-term value creation in a manner consistent with the Company's identity, mission and values;

c. assuring that the interests of the Directors are closely aligned to those of the Company, its business and its stakeholders; and

d. ensuring overall market competitiveness of the Compensation Packages, while providing the Board sufficient flexibility to tailor the Company's compensation practices on a case-by-case basis, depending on the market conditions from time to time.

We believe that this approach and philosophy benefits the realisation of the Company's long-term objectives while keeping with the Company's risk profile.

6.2 Compensation of directors

See Note 20 (*Related parties*) to the consolidated financial statements included in the "**Consolidated Financial Statements**" for an overview of the compensation of the directors in the fiscal year to which this report relates. In determining the level and structure of the compensation of the directors in the fiscal year to which this report relates relevant scenario analyses carried out in advance have been considered.

6.3 Pay ratio

As at 31 December 2020, the Company was not bound by the DCGC, so we are not required to disclose the Company's pay ratio in this report.

7 RELATED PARTY TRANSACTIONS

As at 31 December 2020, the Company was not bound by the DCGC, so the Company is not required to disclose related party transactions in this report.

8 PROTECTIVE MEASURES

We have adopted several provisions that may have the effect of making a takeover of our Company more difficult or less attractive, including:

- the authorization of a class of preferred shares that may be issued to a protective foundation pursuant to a call option to that effect;
- a provision that our directors may only be removed at the general meeting by a two-thirds majority of votes cast representing more than half of our issued share capital if such removal is not proposed by our Board;
- our directors being appointed on the basis of a binding nomination by our Board, which can only be overruled by the general meeting by a resolution adopted by at least a two-thirds majority of the votes cast, provided such majority represents more than half of the issued share capital (in which case the Board shall make a new nomination);
- a provision which allows the former chairman of our Board or our former chief executive officer to be charged with our management if all of our directors are absent or incapacitated; and
- requirements that certain matters, including an amendment of our articles of association, may only be brought to our shareholders for a vote upon a proposal by our Board.

In addition, Dutch law allows for staggered multi-year terms of our directors, as a result of which only part of our directors may be subject to appointment or re-appointment in any one year.

Furthermore, in accordance with the DCGC, shareholders who have the right to put an item on the agenda for our General Meeting or to request the convening of a General Meeting shall not exercise such rights until after they have consulted our Board. If exercising such rights may result in a change in our strategy (for example, through the dismissal of directors), our Board must be given the opportunity to invoke a reasonable period of up to 180 days to respond to the shareholders' intentions. If invoked, our Board must use such response period for further deliberation and constructive consultation, in any event with the shareholder(s) concerned and exploring alternatives. At the end of the response time, our Board shall report on this consultation and the exploration of alternatives to our General Meeting. The response period may be invoked only once for any given General Meeting and shall not apply (i) in respect of a matter for which a response period has been previously invoked or (ii) if a shareholder holds at least 75% of our issued share capital as a consequence of a successful public bid.

In addition, as of May 1, 2021, a statutory cooling-off period of up to 250 days was introduced, during which, if invoked by the Board, our General Meeting would not be able to dismiss, suspend or appoint directors (or amend the provisions in our articles of association dealing with such matters) unless

those matters would be proposed by our Board. This cooling-off period could be invoked by our Board, in case (i) shareholders, using either their shareholder proposal right or their right to request a general meeting, propose an agenda item for the General Meeting to dismiss, suspend or appoint a director (or an amendment to our articles of association dealing with such matters) or (ii) a public offer for our Company is made or announced without our support, provided, in each case, that our Board believes that such proposal or offer materially conflicts with the interests of our Company and its business. In addition to the termination grounds provided under this bill, shareholders representing at least 3% of our issued share capital may request the Enterprise Chamber of the Amsterdam Court of Appeal (the "**Enterprise Chamber**") for early termination of the cooling-off period. The Enterprise Chamber must rule in favor of the request if the shareholders can demonstrate that (i) our Board, in light of the circumstances at hand when the cooling-off period was invoked, could not reasonably have come to the conclusion that the relevant shareholder proposal or hostile public offer constituted a material conflict with the interests of our Company and its business, (ii) our Board cannot reasonably believe that a continuation of the cooling-off period would contribute to careful policy-making or (iii) other defensive measures have been activated for our company during the cooling-off period which have not been terminated or suspended at the relevant shareholders' request within a reasonable period following the request (i.e., no 'stacking' of defensive measures). During a cooling-off period, if invoked, our Board must gather all relevant information necessary for a careful decision-making process. In this context, our Board must at least consult with shareholders representing at least 3% of our issued share capital at the time the cooling-off period was invoked and with the Dutch works council (in case such works council is established). Formal statements expressed by these stakeholders during such consultations must be published on the Company's website to the extent these stakeholders have approved that publication. Ultimately one week following the last day of the cooling-off period, our Board must publish a report in respect of its policy and conduct of affairs during the cooling-off period on our website. This report must remain available for inspection by shareholders and others with meeting rights under Dutch law at our office and must be tabled for discussion at the next General Meeting.

Signature page to the Dutch statutory board report of Pharvaris N.V. for the fiscal year ended December 31, 2020

Leiden, May 31, 2021

_____	_____
B.A.E. Modig	M. Kleijwegt
_____	_____
R.P.L. Droller	R.H. Glassman
_____	_____
J.G.C.P. Schikan	D.P. Meeker

FINANCIAL STATEMENTS

Consolidated Financial Statements

Consolidated statements of profit or loss and other comprehensive income

Years ended December 31,

	Notes	2020	2019	As at January 1, 2019
		€	€	€
Research and development expenses	3	(19,508,101)	(5,684,562)	(3,645,413)
General and administrative expenses	4	(5,498,491)	(2,325,719)	(668,121)
Total operating expenses		(25,006,592)	(8,010,281)	(4,313,534)
Finance expenses	7	(1,062,363)	(16,881)	(380)
Loss before income tax		(26,068,955)	(8,027,162)	(4,313,914)
Income tax benefit	8	83,251	-	-
Loss for the year		(25,985,704)	(8,027,162)	(4,313,914)
Other comprehensive income/(loss)				
Exchange loss arising on translation of foreign operations		(4,365)	-	-
Total comprehensive loss attributable to:				
Equity holders of the Company		(25,990,069)	(8,027,162)	(4,313,914)
Basic and diluted loss per share	19	(5,36)	(1.66)	(0.89)

The accompanying notes are an integral part of these consolidated financial statements

Consolidated statements of financial position

(after appropriation of result)

	Notes	As at December 31, 2020 €	As at December 31, 2019 €	As at January 1, 2019 €
Assets				
Non-current assets				
Property, plant and equipment	9	48,503	12,927	-
Current assets				
Deferred tax assets	8	99,339	-	-
Receivables	10	569,578	210,843	26,423
Other current assets	11	1,753,327	47,536	22,641
Cash and cash equivalents	12	98,628,871	20,326,372	5,385,333
Total assets		101,099,618	20,597,678	5,434,377
Equity and liabilities				
Equity	13			
Share capital		235,693	130,962	100,928
Share premium		138,034,580	36,624,697	15,023,205
Other reserves		1,979,875	392,139	275,992
Currency translation reserve		(4,365)	-	-
Accumulated loss		(44,459,954)	(18,474,250)	(10,447,088)
Total equity		95,785,829	18,673,548	4,953,037
Current liabilities				
Trade and other payables	14	846,952	517,771	246,983
Accrued liabilities	16	4,466,837	1,406,359	234,357
Total liabilities		5,313,789	1,924,130	481,340
Total equity and liabilities		101,099,618	20,597,678	5,434,377

The accompanying notes are an integral part of these consolidated financial statements

Consolidated statements of changes in equity

	Notes	Share capital	Share premium	Other reserves	Currency translation reserve	Accumulated losses	**Total Equity**
		€	€	€	€	€	€
Balance at January 1, 2018		100,928	10,514,354	175,247	-	(6,133,174)	4,657,355
Total comprehensive loss					-	(4,313,914)	(4,313,914)
Issue of share capital		-	4,508,851	-	-	-	4,508,851
Share-based payments				100,745	-	-	100,745
Balance at December 31, 2018		100,928	15,023,205	275,992		(10,447,088)	4,953,037
Balance at January 1, 2019		100,928	15,023,205	275,992	-	(10,447,088)	4,953,037
Total comprehensive loss		-	-	-	-	(8,027,162)	(8,027,162)
Issue of share capital	13	30,034	22,437,673	-	-	-	22,467,707
Transaction costs on issue of shares		-	(836,181)	-	-	-	(836,181)
Share-based payments	18	-	-	116,147	-	-	116,147
Balance at December 31, 2019		130,962	36,624,697	392,139	-	(18,474,250)	18,673,548
Balance at January 1, 2020		130,962	36,624,697	392,139	-	(18,474,250)	18,673,548
Total comprehensive loss		-	-	-	-	(25,985,704)	(25,985,704)
Issue of share capital	13	104,731	102,410,148	-	-	-	102,514,879
Transaction costs on issue of shares		-	(1,000,265)	-	-	-	(1,000,265)
Currency translation reserve		-	-	-	(4,365)	-	(4,365)
Share-based payments	18	-	-	1,587,736	-	-	1,587,736
Balance at December 31, 2020		235,693	138,034,580	1,979,875	(4,365)	(44,459,954)	95,785,829

The accompanying notes are an integral part of these consolidated financial statements

Consolidated statements of cash flows

	Notes	Years ended December 31, 2020	2019	2018
		€	€	€
Operating activities				
Loss before tax		(26,068,955)	(8,027,162)	(4,313,914)
Non-cash adjustments to reconcile loss before tax to net cash flows used in operations:				
Share-based payment expense	5	1,587,736	116,147	100,745
Depreciation expense	8	7,401	549	-
Net foreign exchange (gain) / loss		1,350,592	(3,693)	2,969
Finance costs	6	98,678	-	-
Changes in working capital:				
Increase in receivables		(358,735)	(184,420)	(47,988)
Increase in other current assets	10	(493,165)	(24,915)	-
Increase in trade and other payables		329,181	274,481	182,606
Increase in accrued liabilities		2,094,322	1,172,002	156,929
Paid interest		(46,648)	-	-
Net cash flows used in operating activities		(21,499,593)	(6,677,011)	(3,918,653)
Investing activities				
Purchase of property, plant and equipment	8	(42,977)	(13,476)	-
Net cash flows used in investing activities		(42,977)	(13,476)	-
Financing activities				
Proceeds from issue of shares	12	102,514,879	22,467,707	4,508,851
Transaction costs		(1,314,078)	(836,181)	-
Net cash flows provided by financing activities		101,200,801	21,631,526	4,508,851
Net increase in cash and cash equivalents		79,658,231	14,941,039	590,198
Cash and cash equivalents at the beginning of the year		20,326,372	5,385,333	4,795,135
Effect of exchange rate changes		(1,355,732)	-	-
Cash and cash equivalents at the end of the year	11	98,628,871	20,326,372	5,385,333

The accompanying notes are an integral part of these consolidated financial statements

Notes to the consolidated financial statements

1 Corporate and Group information

This section provides general corporate and group information about Pharvaris N.V. (formerly Pharvaris B.V.) and its subsidiaries. Refer to note 23 for the disclosure on the Company's conversion from a Dutch limited liability company (B.V.) to a Dutch public limited liability company (N.V.).

1.1 Corporate information

The consolidated financial statements of Pharvaris N.V. (the "Company" or "Pharvaris") and its subsidiaries (collectively, "The Group") for the year ended December 31, 2020 were authorized for issue in accordance with a resolution of the directors on May 26, 2021.

Pharvaris N.V. was incorporated on September 30, 2015 and is based in Leiden, the Netherlands. The address of its registered office is J.H. Oortweg 21, Leiden. It has been registered at the Chamber of Commerce under file number 64239411.

Pharvaris N.V. is a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapies for rare diseases with significant unmet need, initially focused on angioedema and other bradykinin-mediated diseases.

1.2 Group information

Subsidiaries

The consolidated financial statements of the Group include:

Name	Legal seat	Country of incorporation	% of equity interest	
			2020	2019
Pharvaris Holdings B.V.	Leiden	The Netherlands	100%	100%
Pharvaris Netherlands B.V.	Leiden	The Netherlands	100%	100%
Pharvaris, Inc.	Delaware	United States of America	100%	n/a
Pharvaris GmbH	Zug	Switzerland	100%	n/a

Pharvaris, Inc. and Pharvaris GmbH were incorporated on January 31, 2020 and March 27, 2020, respectively. Pharvaris, Inc. acts as a service provider to the principal Company of the Group. Pharvaris GmbH is the principal Company of the Group starting April 1, 2020. The principal Company faces the market/external parties and making all operational group decisions.

The ultimate parent company
The ultimate parent company of the Group is Pharvaris N.V., which is based in the Netherlands.

2. Summary of significant accounting policies

2.1 Basis of preparation

The consolidated financial statements of the Group have been prepared in accordance with International Financial Reporting Standards as adopted by the European Union (IFRS-EU) and with Part 9 of Book 2 of the Dutch Civil Code.

The consolidated financial statements have been prepared on a historical cost basis. Unless otherwise stated, the consolidated financial statements are presented in Euro and all values are rounded to the nearest EUR (€), except per share amounts.

Since Pharvaris N.V's statement of profit or loss for 2020 is recognized in the consolidated financial statements, it is sufficient in the company financial statements to present a condensed statement of profit or loss in accordance with section 402 of Book 2 of the Dutch Civil Code.

2.2 Going concern

Pharvaris is a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapies for rare diseases with significant unmet need, initially focused on angioedema. These therapies will need to go through clinical development trials to achieve regulatory approval for commercialization. Therefore, Pharvaris is incurring annual research and development and other operating costs and has no revenues to date (as is typical in the biotech industry for development stage and early commercial stage companies). As such, Pharvaris anticipates on-going negative operating cash flows for several years before the company has a product candidate ready for commercialization, if proven successful. This makes the Group dependent on external capital sources, debt capital and equity capital. The Group is currently fully financed by equity capital.

The Group had cash of €98.6 million, €20.3 million and €5.4 million as of December 31, 2020, 2019 and 2018 respectively. The Group incurred net losses of €26.0 million in 2020, €8.0 million in 2019 and €4.3 million in 2018 and negative operating cash flows of €21.5 million, €6.7 million and € 3.9 million in 2020, 2019 and 2018, respectively.

The Group does not expect positive operating cash flows in the foreseeable future and remains dependent on additional financing to fund its research and development expenses, general and administrative expenses and financing costs. However, the Group believes that the available cash balances are sufficient to execute the Group's operating plan and strategies and to meet the anticipated working capital requirements and settle all expected liabilities for a period of at least twelve months after the signing date of these financial statements. Accordingly, the consolidated financial statements have been prepared on a going concern basis.

Impact of COVID-19

The outbreak of a novel strain of the coronavirus, specifically identified as "COVID-19", has spread globally. COVID-19 is a virus causing potentially deadly respiratory tract infections and has impacted the global economy. In March 2020, the World Health Organization declared COVID-19 a pandemic.

The Group has taken appropriate measures to protect the safety of the employees and continuously monitors and evaluates the situation regarding COVID-19. The COVID-19 outbreak has delayed, and may continue to delay, enrollment in our clinical trials. The Group experienced an approximate two-month delay in starting the enrollment of our now completed Phase 1 multiple ascending dose study of PHA121 in healthy volunteers as a result of COVID-19.

The spread of an infectious disease, including COVID-19, may also result in the inability of our suppliers to deliver components or raw materials, and the inability of our CDMOs to provide supplies of our product candidates for our planned clinical trials, on a timely basis or at all. Further, it may impact the ability of our CROs, including non-clinical CROs, to provide services to support our clinical program. The extent to which the COVID-19 pandemic impacts our business will depend on future developments, which are uncertain and cannot be predicted, including new information which may emerge concerning the severity of the COVID-19 pandemic and the actions to contain COVID-19 or treat its impact, among others. If we are unable to meet our milestones it might jeopardize our funding opportunities.

In addition, the COVID-19 pandemic has already caused, and is likely to result in further, significant disruptions and uncertainties in global financial markets, which may reduce our ability to access capital on favorable terms or at all. A recession, depression or other sustained adverse market event resulting from the spread of COVID-19 could also materially and adversely affect our business and the value of our ordinary shares.

The Group continuously monitors the situation regarding COVID-19, and the possible impact on the CROs, contract manufacturing organizations and clinical sites performing research and development activities for the Group. All efforts are made to develop alternatives to limit the impact of COVID-19 going forward.

The ultimate impact of the COVID-19 pandemic is uncertain and subject to change. However, management does not expect that COVID-19 will have a material adverse effect on the financial condition or liquidity of the Company.

2.3 Basis of consolidation

Subsidiaries are entities controlled by the Company. The Company controls an entity when it is exposed to, or has rights to, variable returns from its involvement with the entity and has the ability to affect those returns through its power over the entity. The financial statements of subsidiaries are included in the consolidated financial statements from the date on which control commences until the date on which control ceases. Intra-group balances and transactions are eliminated in the consolidation.

2.4 Segment reporting

Operating segments are identified based on whether the allocation of resources and/ or the assessment of performance of a particular component of Group's activities are regularly reviewed as a separate operating segment by Group's Chief Operating Decision Maker ("CODM"). By these criteria, the activities of Pharvaris are considered to be one segment which comprises the discovery, development and commercialization of oral bradykinin B2 receptor antagonists and the segmental analysis is the same as the analysis for Pharvaris as a whole. The Board of directors is identified as the CODM and reviews the consolidated operating results regularly to make decisions about the resources and to assess overall performance.

2.5 Foreign currencies

Items included in the financial statements of each of the group's entities are measured using the currency of the primary economic environment in which the entity operates. The Group's consolidated financial statements are presented in Euro, which is also the Company's functional currency.
Transactions and balances
Transactions in foreign currencies are initially recorded by the Group's entities at their respective functional currency spot rates at the date the transaction first qualifies for recognition.

Monetary assets and liabilities denominated in foreign currencies are translated at the functional currency spot rates of exchange at the reporting date. Differences arising on settlement or translation of monetary items are recognized in profit or loss.

Non-monetary items that are measured in terms of historical cost in a foreign currency are translated using the exchange rates at the dates of the initial transactions.

Upon consolidation, the assets and liabilities of foreign operations are translated into Euro at the rate of exchange prevailing at the reporting date and their statements of operations are translated at the average exchange rate of the fiscal period. The exchange differences arising on translation for consolidation are recognized directly in other comprehensive income.

2.6 Notes to the cash flow statement

The cash flow statement has been prepared using the indirect method. The cash and cash equivalents disclosed in the cash flow statement comprises of cash at bank.

2.7 Property, Plant and Equipment

Property, plant and equipment comprises office equipment. Property, plant and equipment are stated at historical

cost less accumulated depreciation. Historical cost includes expenditure that is directly attributable to the acquisition of the items. Subsequent costs are included in the asset's carrying amount or recognized as a separate asset only when it is probable that future economic benefits associated with the item will flow to the Group and the cost of the item can be measured reliably.

Depreciation on property, plant and equipment is calculated using the straight-line method to allocate their cost over their estimated useful lives, as follows:
Office equipment 3-5 years

The assets' residual values and useful lives are reviewed, and adjusted if appropriate, at each balance sheet date. An asset's carrying amount is written down immediately to its recoverable amount if the asset's carrying amount is larger than its estimated recoverable amount.

Gains and losses on disposals are determined by comparing proceeds with the carrying amount and are recognized in the consolidated statements of profit or loss and other comprehensive income.

2.8 Financial instruments Recognition and measurement

Financial assets

Initial recognition and measurement

Financial assets are initially measured at fair value. After the initial measurement, the financial assets are subsequently classified as either measured at amortized cost, fair value through the consolidated statements of profit or loss and comprehensive income.

The classification of financial assets at initial recognition depends on the financial asset's contractual cash flow characteristics and the Group's business model for managing them. The Group initially measures a financial asset at its fair value. Financial assets are included in Group's consolidated statements of financial position when Pharvaris becomes a party to the contractual provisions of the instrument.

Subsequent measurement

Financial assets are subsequently measured at amortized cost. Financial assets at amortized cost are subsequently measured using the effective interest method and are subject to impairment. Gains and losses are recognized in the consolidated statements of profit or loss and other comprehensive income when the asset is derecognized, modified or impaired.

For the year ended December 31, 2020, the Group had the following financial assets to be measured at amortized cost:

- Cash and cash equivalents
- Receivables

Derecognition
Financial assets are derecognized when the rights to receive cash flows from the investments have expired or have been transferred and where the Group has transferred substantially all risks and rewards of ownership.

Financial liabilities

Initial recognition and measurement

Financial liabilities are classified, at initial recognition, as financial liabilities at fair value through other comprehensive income, or fair value through the consolidated statements of profit or loss and other comprehensive income, as payables.

All financial liabilities are recognized initially at fair value and, in the case of loans and borrowings and payables, net of directly attributable transaction costs. The Group's financial liabilities include trade payables and accrued liabilities.

Subsequent measurement

After initial recognition, trade payables and accrued liabilities are subsequently measured at amortized cost. Gains and losses are recognized in the consolidated statements of profit or loss and other comprehensive income.

Derecognition

A financial liability is derecognized when the obligation under the liability is discharged or cancelled or is expired.

2.9 Receivables

Receivables are recognized initially at fair value and subsequently measured at amortized cost. If payment of the receivable is postponed under an extended payment deadline, fair value is measured on the basis of the discounted value of the expected payments. When a receivable is uncollectible, it is written off against the allowance account for receivables.

2.10 Cash and cash equivalents

Cash and cash equivalents comprise bank balances.

2.11 Equity

The Group classifies an instrument, or its component parts, on initial recognition as a financial liability or an equity instrument in accordance with the substance of the contractual arrangement and the definitions of a financial liability and an equity instrument.

An instrument is classified as a financial liability when it is either (i) a contractual obligation to deliver cash or another financial asset to another entity or to exchange financial assets or financial liabilities with another entity under conditions that are potentially unfavorable to the Group; or (ii) a contract that will or may be settled in the Group's own equity instruments and is a non-derivative for which the Group is or may be obliged to deliver a variable number of the Group's own equity instruments or a derivative that will or may be settled other than by the exchange of a fixed amount of cash or another financial asset for a fixed number of the Group's own equity instruments. An equity instrument is defined as any contract that evidences a residual interest in the assets of an entity after deducting all of its liabilities. An instrument is an equity instrument only if the issuer has an unconditional right to avoid settlement in cash or another financial asset.

Ordinary shares

Ordinary shares are classified as equity.

Preferred shares

Preferred shares are equity classified as result of:

- The lack of contractual obligation to deliver cash or another financial asset to another entity, or to exchange financial assets or financial liabilities with another entity under conditions that are potentially unfavorable to the Group.
- No contractual obligation to transfer an amount (dividend) independent of the entity's available economic resources.

Pursuant to the shareholders' agreement, all of the outstanding preferred shares will automatically convert into ordinary shares upon the consummation of a qualified Initial Public Offering (IPO) or on request of the majority of the issued and outstanding preferred shares. The conversion rate for the preferred shares is calculated by reference to the original issue price of relevant preferred shares, adjusted for certain anti-dilution protections.

The holders of the outstanding preferred shares are entitled to convert the preferred shares, at any time, without payment of additional consideration into ordinary shares at a conversion rate of 1:1 which conversion rate shall

be adjusted so as to reflect this ratio after any amendment of the nominal value by means of any stock splits, reclassification of shares and similar events.

The Group issued three classes of preferred shares, convertible preferred shares A, the convertible preferred shares B and the convertible preferred shares C. The dividend preference is noncumulative and is only applicable when the general meeting of shareholder's decides to make a profit distribution (Note 13).

Convertible Preferred shares A, convertible preferred shares B and convertible preferred shares C

Preferred shares A, preferred shares B and preferred shares C have a dividend preference over ordinary shares. In addition, preferred shares A, preferred shares B and preferred shares C have an anti-dilution protection that is not applicable for ordinary shares. The anti-dilution protection is under the full control of the Group and does not affect the equity classification of the preferred shares A, preferred shares B and preferred shares C.

Preferred shares A, preferred shares B and preferred shares C qualify as equity. Dividends paid on the preference shares are treated as profit appropriation.

2.12 Trade and other payables

Trade and other payables are obligations to pay for goods or services that have been acquired in the ordinary course of business from suppliers. Accounts payable are classified as current liabilities if payment is due within one year or less (or in the normal operating cycle of the business if longer). If not, they are presented as non-current liabilities.

Trade and other payables are recognized initially at fair value and subsequently measured at amortized cost using the effective interest method.

2.13 Current and deferred income tax

The tax expense for the period comprises current and deferred tax. Tax effects are recognized in the consolidated statements of income or loss and comprehensive income, except to the extent that it relates to items recognized in other comprehensive income or directly in equity.

The current income tax charge is calculated on the basis of the tax laws enacted or substantively enacted at the balance sheet date in the countries where the Company's subsidiaries operate and generate taxable income. Management periodically evaluates positions taken in tax returns with respect to situations in which applicable tax regulation is subject to interpretation. It establishes provisions where appropriate on the basis of amounts expected to be paid to the tax authorities.

Deferred income tax is recognized, using the liability method, on temporary differences arising between the tax basis of assets and liabilities and their carrying amounts in the consolidated financial statements. Deferred income tax is determined using tax rates (and laws) that have been enacted or substantially enacted by the balance sheet date and are expected to apply when the related deferred income tax asset is realized or the deferred income tax liability is settled.

Deferred income tax assets are recognized only to the extent that it is probable that future taxable profit will be available against which the temporary differences can be utilized.

Deferred income tax assets and liabilities are offset when there is a legally enforceable right to offset current tax assets against current tax liabilities and when the deferred income tax assets and liabilities relate to income taxes levied by the same taxation authority on either the taxable entity or different taxable entities where there is an intention to settle the balances on a net basis.

2.14 Share-based payment

The Company operates an equity-settled share-based compensation plan, under which it receives services as consideration for equity instruments (options or restricted stock units) of the Company. The fair value of these equity instruments granted in exchange for the services received from the participants is recognized as an expense against a credit in equity. The total amount to be expensed is determined by reference to the grant date fair value of the equity instruments granted, including the impact of any market performance vesting conditions and non-vesting conditions.

Service and non-market performance vesting conditions are included in the assumptions about the number of equity instruments that are expected to vest. The total expense is recognized over the vesting period, which is the period over which all of the specified vesting conditions are to be satisfied. If the length of the vesting period varies depending on when a non-market performance condition is satisfied, the total expense is recognized over the expected vesting period. The Group recognizes the impact of the revision to previous estimates, if any, in the consolidated statements of profit or loss and other comprehensive income, with a corresponding adjustment to equity.

When options are exercised, the Company issues new shares. The proceeds received net of any directly attributable transaction costs are credited to share capital (nominal value) and share premium when the options are exercised.

2.15 Expenses

Research and development expenses

Research activities undertaken with the prospect of gaining new scientific knowledge and understanding are expensed as incurred. Development expenses are capitalized only if the cost involved can be measured reliably, the product or process under development is technically feasible, future economic benefits are probable and the Group has the intention and resources to complete development and use or sell it. Due to the regulatory environment and other types of uncertainty, management has determined that the criteria for capitalizing development costs to intangible assets, as set out in IAS 38, have not been met and therefore the Group has not capitalized any development expenses in 2020 or 2019. See Note 4 for information relating to research and development expenses incurred in the reporting period.

At each balance sheet date, the Group estimates the level of services performed by the vendors and the associated cost incurred for the services performed.

General and administrative expenses

Expenses are recognized in Group’s consolidated statements of profit or loss and other comprehensive income as expenses when incurred.

Personnel expenses

Wages and salaries, social security contributions, paid leave and bonuses, and other employee benefits are recognized in the financial year in which the employee provide the associated services.

The group's pension plans are classified as defined contribution plans, and, accordingly, no pension obligations are recognized in the balance sheet. Costs relating to defined contribution plans are included in the income statement in the period in which they are incurred, and outstanding contributions are included in other payables.

2.16 New and amended standards and interpretations

Definition of a Business - Amendments to IFRS 3
The IASB issued amendments to the definition of a business in IFRS 3 Business Combinations to help entities determine whether an acquired set of activities and assets is a business or not. They clarify the minimum requirements for a business, remove the assessment of whether market participants are capable of replacing any missing elements, add guidance to help entities assess whether an acquired process is substantive, narrow the definitions of a business and of outputs, and introduce an optional fair value concentration test. New illustrative examples were provided along with the amendments.
The amendments must be applied to transactions that are either business combinations or asset acquisitions for which the acquisition date is on or after the beginning of the first annual reporting period beginning on or after January 1, 2020. Consequently, entities do not have to revisit such transactions that occurred in prior periods.
The Group has assessed amendments IFRS 3’s full impact and concludes that the amendments to the definition of a business in IFRS to have no impact on Group’s consolidated financial statements.

Definition of Material - Amendments to IAS 1 and IAS 8
In October 2018, the IASB issued amendments to IAS 1 Presentation of Financial Statements and IAS 8 to align the definition of ‘material’ across the standards and to clarify certain aspects of the definition. The new definition

states that, 'Information is material if omitting, misstating or obscuring it could reasonably be expected to influence decisions that the primary users of general purpose financial statements make on the basis of those financial statements, which provide financial information about a specific reporting entity.'

The amendments clarify that materiality will depend on the nature or magnitude of information, or both. An entity will need to assess whether the information, either individually or in combination with other information, is material in the context of the financial statements.

Although the amendments to the definition of material is not expected to have a significant impact on an entity's financial statements, the introduction of the term 'obscuring information' in the definition could potentially impact how materiality judgements are made in practice, by elevating the importance of how information is communicated and organized in the financial statements.

The amendments are effective for annual periods beginning on or after January 1, 2020 and are applied prospectively. The Group has assessed the amendments to IAS 1 and IAS 8's full impact and concludes that the amendments have no material effect on Group's consolidated financial statements.

IFRS 16 Leases: Covid-19-Related Rent Concessions
In May 2020, the International Accounting Standards Board (Board) issued Covid-19-Related Rent Concessions, which amended IFRS 16 Leases. The amendment permits lessees, as a practical expedient, not to assess whether particular rent concessions occurring as a direct consequence of the covid-19 pandemic are lease modifications and instead to account for those rent concessions as if they are not lease modifications.

The amendment is effective on June 30, 2020 and has been adopted by the Group. The Group has assessed the amendment of IFRS 16 Leases' full impact and concludes that the amendment has no effect on the Group's consolidated financial statements.

2.17 Standards issued but not yet effective

The standards and interpretations that are issued, but not yet effective, up to the date of issuance of the Group's financial statements are disclosed below. The Group intends to adopt these standards, if applicable, when they become effective.

Amendments to IAS 1: Classification of Liabilities as Current or Non-current

In January 2020, the IASB issued amendments to paragraphs 69 to 76 of IAS 1 to specify the requirements for classifying liabilities as current or non-current. The amendments clarify:

- What is meant by a right to defer settlement
- That a right to defer must exist at the end of the reporting period
- That classification is unaffected by the likelihood that an entity will exercise its deferral right
- That only if an embedded derivative in a convertible liability is itself an equity instrument would the terms of a liability not impact its classification

The amendments are effective for annual reporting periods beginning on or after 1 January 2023 and must be applied retrospectively. The amendments are not expected to have a material impact on the Group.

Reference to the Conceptual Framework – Amendments to IFRS 3
In May 2020, the IASB issued Amendments to IFRS 3 Business Combinations - Reference to the Conceptual Framework. The amendments are intended to replace a reference to the Framework for the Preparation and Presentation of Financial Statements, issued in 1989, with a reference to the Conceptual Framework for Financial Reporting issued in March 2018 without significantly changing its requirements.

The IASB also added an exception to the recognition principle of IFRS 3 to avoid the issue of potential 'day 2' gains or losses arising for liabilities and contingent liabilities that would be within the scope of IAS 37 or IFRIC 21 Levies, if incurred separately. At the same time, the IASB decided to clarify existing guidance in IFRS 3 for contingent assets that would not be affected by replacing the reference to the Framework for the Preparation and Presentation of Financial Statements.

The amendments are effective for annual reporting periods beginning on or after 1 January 2022 and apply prospectively.

Property, Plant and Equipment: Proceeds before Intended Use – Amendments to IAS 16
In May 2020, the IASB issued Property, Plant and Equipment — Proceeds before Intended Use, which prohibits entities deducting from the cost of an item of property, plant and equipment, any proceeds from selling items produced while bringing that asset to the location and condition necessary for it to be capable of operating in the manner intended by management. Instead, an entity recognizes the proceeds from selling such items, and the costs of producing those items, in profit or loss.

The amendment is effective for annual reporting periods beginning on or after 1 January 2022 and must be applied retrospectively to items of property, plant and equipment made available for use on or after the beginning of the earliest period presented when the entity first applies the amendment. The amendments are not expected to have a material impact on the Group.

Onerous Contracts – Costs of Fulfilling a Contract – Amendments to IAS 37
In May 2020, the IASB issued amendments to IAS 37 to specify which costs an entity needs to include when assessing whether a contract is onerous or loss-making.

The amendments apply a "directly related cost approach". The costs that relate directly to a contract to provide goods or services include both incremental costs and an allocation of costs directly related to contract activities. General and administrative costs do not relate directly to a contract and are excluded unless they are explicitly chargeable to the counterparty under the contract.

The amendments are effective for annual reporting periods beginning on or after 1 January 2022. The Group will apply these amendments to contracts for which it has not yet fulfilled all its obligations at the beginning of the annual reporting period in which it first applies the amendments.

IFRS 9 Financial Instruments – Fees in the '10 per cent' test for derecognition of financial liabilities
As part of its 2018-2020 annual improvements to IFRS standards process the IASB issued amendment to IFRS9. The amendment clarifies the fees that an entity includes when assessing whether the terms of a new or modified financial liability are substantially different from the terms of the original financial liability. These fees include only those paid or received between the borrower and the lender, including fees paid or received by either the borrower or lender on the other's behalf. An entity applies the amendment to financial liabilities that are modified or exchanged on or after the beginning of the annual reporting period in which the entity first applies the amendment.

The amendment is effective for annual reporting periods beginning on or after 1 January 2022 with earlier adoption permitted. The Group will apply the amendments to financial liabilities that are modified or exchanged on or after the beginning of the annual reporting period in which the entity first applies the amendment. The amendments are not expected to have a material impact on the Group.

2.18 Significant accounting judgements, estimates and assumptions

The preparation of the Group's consolidated financial statements requires management to make judgements, estimates and assumptions that affect the reported amounts of expenses, income, assets and liabilities, and the accompanying disclosures. Uncertainty about these assumptions and estimates could result in outcomes that require a material adjustment to the carrying amount of assets or liabilities affected in future periods.

In the process of applying the Group's accounting policies, management has made various judgements. Those which management has assessed to have the most significant effect on the amounts recognized in the financial statements have been discussed below.

The key assumptions concerning the future and other key sources of estimation uncertainty at the reporting date, that have a significant risk of causing a material adjustment to the carrying amounts of assets and liabilities within the next financial year, are also described in the individual notes. The Group based its assumptions and estimates on parameters available when the consolidated financial statements were prepared. Existing circumstances and assumptions about future developments, however, may change due to market changes or

circumstances arising that are beyond the control of the Group. Such changes are reflected in the assumptions when they occur.

Share-based payments

The Group has adopted an equity-settled share-based compensation plan, pursuant to which certain participants are granted the right to acquire ordinary shares of the Company. The grants made under this plan are accounted for in accordance with the policy as stated in Note 2.14. The total amount to be expensed is determined by reference to the fair value of the options or restricted stock units granted. The fair value is measured at the date of grant using an Option Pricing model as further explained in Note 18.

Due to the lack of quoted market prices, the Group has determined the fair value for the measurement of the equity-settled transactions at the grant date with assistance of an external appraiser, considering certain assumptions relating to the volatility of stock price, the determination of an appropriate risk-free interest rate and expected dividends.

Research and development expenses

Research and development expenses are currently not capitalized but are expensed because the criteria for capitalization are not met (Note 2.15 and Note 4). At each balance sheet date, the Group estimates the level of services performed by the vendors and the associated costs incurred for the services performed. Although we do not expect the estimates to be materially different from amounts actually incurred, the understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in reporting amounts that are too high or too low in any particular period.

3. First-time adoption of IFRS

The financial statements for the year ended December 31, 2020, are the first the Group has prepared in accordance with IFRS as adopted by the European Union (IFRS-EU). For periods up to and including the year ended December 31, 2019, the Group prepared its consolidated financial statements in accordance with the provisions of Title 9, Book 2 of the Dutch Civil Code and the firm pronouncements in the Dutch Accounting Standards, as published by the Dutch Accounting Standards Board (‘Raad voor de Jaarverslaggeving’) (Dutch GAAP) as local generally accepted accounting principles.

Accordingly, the Group has prepared consolidated financial statements that comply with IFRS-EU as at December 31, 2020, together with the comparative period data for the year ended December 31, 2019. In preparing the financial statements, the Group’s opening statement of financial position was prepared as at January 1, 2019, the Group’s date of transition to IFRS-EU.

There were no differences identified by the Group in translating its Dutch GAAP financial statements, including the statement of financial position as at 1 January 2019 and the financial statements as of, and for, the year ended 31 December 2019.

4. Research and development expenses

	2020	2019	2018
	€	€	€
Personnel expenses (Note 6)	(2,951,323)	(131,544)	(99,946)
Clinical expenses	(8,748,748)	(2,009,892)	(205,873)
Pre-clinical expenses	(3,322,590)	(1,850,444)	(2,449,046)
Manufacturing costs	(4,311,958)	(1,379,590)	(870,933)
License costs	-	(300,000)	-
Intellectual Property costs	(173,482)	(13,092)	(19,615)
	(19,508,101)	(5,684,562)	(3,645,413)

Development expenses are currently not capitalized but are recorded in consolidated statements of profit or loss and other comprehensive income because the recognition criteria for capitalization are not met.

Clinical expenses include costs of conducting and managing our sponsored clinical trials, including clinical investigator cost, costs of clinical sites, and costs for CRO's assisting with the clinical development programs.

Pre-clinical expenses include costs of our outsourced discovery, preclinical and nonclinical development studies.

Manufacturing expenses include costs related to manufacturing of active pharmaceutical ingredients and manufacturing of the products used in our clinical trials and research and development activities.

5. General and administrative expenses

	2020	2019	2018
	€	€	€
Personnel expenses (Note 6)	(1,490,674)	(49,601)	(799)
Consulting fees	(1,042,195)	(990,730)	(333,160)
Professional fees	(943,322)	(495,326)	(62,958)
Accounting, tax and auditing fees	(1,275,842)	(300,841)	(111,852)
Travel expenses	(26,773)	(236,904)	(47,536)
Facilities, communication & office expenses	(551,223)	(167,062)	(84,970)
Other expenses	(168,462)	(85,255)	(26,846)
	(5,498,491)	(2,325,719)	(668,121)

In 2020 the Group entered into a number of lease arrangements, which were assessed to be short-term leases (with a lease term of maximum 12 months equaling its non-cancellable period). The total outflow for the leases in 2020 was €119,627 (2019 and 2018: €78,897 and €0 respectively) and is included in the Facilities, communication & office expenses.

Depreciation expenses of €7,401 (2019 and 2018: €549 and €0 respectively) is included in the other expenses line.

6. Personnel expenses

	2020	2019	2018
	€	€	€
Wages and salaries	(2,597,270)	(50,573)	-
Pension charges	(72,153)	(1,750)	-
Other social security charges	(184,838)	(12,675)	-
Share-based payments	(1,587,736)	(116,147)	(100,745)
	(4,441,997)	(181,145)	(100,745)

The average number of staff (in FTEs) employed by the Group in 2020 was 9 (2019 and 2018: 3 and 0 respectively).

7. Finance expenses

	2020	2019	2018
	€	€	€
Foreign exchange differences	(963,685)	(10,707)	(380)
Interest expenses over bank balances	(92,470)	(4,377)	-
Other finance expenses	(6,208)	(1,797)	-
	(1,062,363)	(16,881)	(380)

8. Income taxes

	2020	2019	2018
	€	€	€
Current income tax expense	(16,088)	-	-
Deferred tax benefit	99,339	-	-
Income tax benefit	83,251	-	-

The Company and its subsidiaries are in a loss-making position so there was no tax charge or income recognized in the years 2019 and 2018. The tax benefit over the year ended December 31, 2020 relates to a temporary difference in the Company's US subsidiary for which a deferred tax asset is recognized, partly offset by the current tax charges relating to the Company's US subsidiary as the result of a cost-plus agreement between the US entity and Group's principal entity resulting in a taxable profit in the United States of America.

Reconciliation of income tax benefit at statutory tax rate and the income tax benefit as reported in the consolidated statement of profit or loss and other comprehensive income is as follows:

	2020	2019	2018
	€	€	€
Loss before income tax	(26,068,955)	(8,027,162)	(4,313,914)
Income tax benefit at statutory income tax rate of 25%	(6,517,239)	(2,006,791)	(1,078,479)
Recognition of previously unrecognized deferred tax assets	(1,629,392)	-	-
Temporary differences for which no deferred tax assets/liabilities have been recognized	-	1,421,141	789,502
Non-deductible expenses for tax purposes (share based payments)	74,579	4,050	200
Current year losses for which no deferred tax asset has been recognised	3,132,076	580,475	287,652
Differences in overseas tax rates	4,855,980	-	-
Other	745	1,125	1,125
Income tax benefit	(83,251)	-	-

The effect of current year losses for which no DTA has been recognized includes the offsetting effect from the derecognition of losses reported through equity/ consolidated statement of profit or loss and other comprehensive income.

The differences in the overseas tax rates are mainly due to the lower tax rate in Switzerland compared to the statutory income tax rate in the NetherlandsThe effective tax rate is 0.3% (2019 and 2018: 0%).
Pharvaris N.V. is the head of the fiscal unity including Pharvaris Netherlands B.V. and Pharvaris Holdings B.V.

The Group has tax loss carry-forwards of approximately €43.3 million (2019: €5.9 million and 2018 €2.7 million), that are available for offsetting against future taxable profits of the companies in which the losses arose. Under Dutch tax law, for years prior to 2019, profits in a given year can be offset against tax loss carry forwards for up to nine years. In 2019, the Dutch tax law was revised to limit the carry forward period to six years. Under Swiss law, losses can be offset against future income or capital gains for seven years.

Tax loss carry-forwards incurred in current and prior years will expire as follows:

Year	Switzerland	Netherlands	Tax losses
	€ million	€ million	€ million
2025	-	3.9	3.9
2026	-	4.4	4.4
2027	33.8	1.2	35.0
Total carry-forward losses	33.8	9.5	43.3

Deferred tax

Deferred tax assets relating to losses carried forward have not been recognized, and deferred tax assets on deductible temporary differences in excess of deferred tax liabilities on taxable temporary differences have not been recognized in the consolidated statement of profit or loss and other comprehensive income. Deferred taxes have been recognized to the extent that management concludes that there is sufficient probability as per IAS 12 that there will be future taxable profits available in the foreseeable future against which the unused tax losses can be utilized.

Movements in deferred tax balances

	R&D expenses	Other receivables	Accrued expenses	**Total**
	€	€	€	€
Deferred tax assets				
At January 1, 2020	-	-	-	-
(Charged)/credited				
- Profit or loss	1,964,583	-	99,339	**2,063,922**
At December 31, 2020	1,964,583	-	99,339	**2,063,922**
Deferred tax liability				
At January 1, 2020	-	-	-	-
(Charged)/credited				
- Profit or loss	-	(1,964,583)	-	**(1,964,583)**
At December 31, 2020	-	(1,964,583)	-	**(1,964,583)**
Net deferred tax assets at December 31,2020				**99,339**

The total unrecognized deferred tax assets from temporary differences amounts to €0.9 million (2019 and 2018: €2.9 million and €1.6 million, respectively.).

9. Property, plant and equipment

		2020	2019
Net book value	Notes	€	€
As of January 1,		12,927	-
Additions		42,977	13,476
Depreciation expenses	5	(7,401)	(549)
As of December 31,		48,503	12,927

Cumulative depreciation	2020	2019
	€	€
As of January 1,	(549)	-
Depreciation	(7,401)	(549)
As of December 31,	(7,950)	(549)

Cumulative Costs	2020	2019
	€	€
As of January 1,	13,476	-
Additions	42,977	13,476
As of December 31,	56,453	13,476

The Group had no property, plant and equipment at December 31, 2018.

10. Receivables

	2020	2019	2018
	€	€	€
VAT receivables	569,578	210,843	26,423
	569,578	210,843	26,423

11. Other current assets

	2020	2019	2018
	€	€	€
Prepayments	540,701	47,536	22,641
Other assets	1,212,626	-	-
	1,753,327	47,536	22,641

Prepayments mainly relate to prepaid rent, insurance, prepaid personnel expenses and general and administrative expenses.

Other assets mainly consist of deferred transaction costs related to Group's in-process equity financing. The Company defers the transaction costs related to any in-process financing. Upon completion of the financing transactions, all related transaction costs are deducted from share premium.

12. Cash and cash equivalents

	2020	2019	2018
	€	€	€
Cash and cash equivalents	98,628,871	20,326,372	5,385,333
	98,628,871	20,326,372	5,385,333

The Cash and cash equivalents consist of bank balances and are not subject to any restriction.

13. Equity

The capital of the Company is divided into Ordinary shares, preferred shares A, B and C respectively. The nominal value of each share is one eurocent (€0.01). Preferred shares A, B and C are convertible into Ordinary shares. All issued shares are fully paid.

Issued shares

	2020	2019	2018
Preferred shares A	5,242,850	5,242,850	5,242,850
Preferred shares B	7,650,147	3,003,391	-
Preferred shares C	5,826,279	-	-
Ordinary shares	4,850,000	4,850,000	4,850,000
	23,569,276	13,096,241	10,092,850

The Company issued 4,646,756 preferred shares B and 5,826,279 preferred shares C in July 2020 and November 2020, with total proceeds of €35,032,758 and €67,482,121, respectively.

Holders of preferred shares A, B and C shall be entitled to a non-cumulative, non-compounded dividend of 8% per annum of aggregate subscription price paid on such preferred shares A, B and respectively, subject to appropriate adjustment in the event of any dividend, share split, combination or similar recapitalization with respect to such preferred shares. Dividend distribution is at discretion of the Board of the Group. No dividend was distributed in 2020, in 2019 or in 2018.

Preferred shares A, B and C shares have an anti-dilution protection. In the event of an issue of shares to any person, at a price per such share which is lower than the applicable subscription price paid for the preferred shares A, preferred shares B or preferred shares C respectively then the Company shall issue, in accordance with applicable requirements to each of holder of preferred shares, such number of new shares, based upon a broad-based weighted average anti-dilution adjustment, which reduces the subscription price of the relevant preferred shares, to a weighted average price.

The anti-dilution protection is under the full control of the Company and does not affect the equity classification of the preferred shares A, preferred shares B and preferred shares C.

The following describes the nature and purpose of each reserve within equity:

Share premium

The amount subscribed for share capital in excess of nominal value.

Other reserves

Other reserves entirely consist of share-based payments reserve, which is used to recognize: the grant date fair value of options issued but not vested and the grant date fair value of RSUs issued to employees and consultants.

14. Trade and other payables

	2020	2019	2018
	€	€	€
Trade payables	656,448	509,948	246,356
Tax and social security liabilities	190,504	7,823	627
	846,952	517,771	246,983

15. Financial assets and liabilities fair value

Fair values of cash, receivables, and current liabilities approximate their carrying amounts due to the short-term maturities of these instruments.

16. Accrued liabilities

	2020	2019	2018
	€	€	€
Consulting, professional and audit liability	1,505,304	436,768	129,243
Clinical accrued liabilities	635,820	357,719	-
Manufacturing accrued liabilities	970,587	283,115	-
Pre-clinical accrued liabilities	421,429	275,460	104,549
Personnel related accruals	875,238	-	-
Other accrued liabilities	58,459	53,297	565
	4,466,837	1,406,359	234,357

17. Financial risk management

The Group's principal financial instruments consist of receivables, trade and other trade payables. The financial instruments represent the Group's working capital to serve the Group's day-to-day operations.

The Group is exposed to market risk (including currency risk, interest rate risk and price risk), credit risk and liquidity risk. The Group's management manages each risk as discussed below.

Market risk

Currency risk

The Group operates internationally and is exposed to currency risk arising from various currency exposure, primarily with respect to the British pound and the US Dollar as the Group has agreements with Contract Research Organizations ('CRO's) which are based in Great Britain, and consulting agreements with parties that are based in the United States of America and Switzerland. From these transactions, currency risk arises. No formal policy has been set-up to manage the currency risk against the functional currency of the Group. As of December 31, 2020, the amount of trade payables in foreign currency was limited. Foreign currency trade payables are short term in nature (generally 30 days). The Group keeps an amount of €27.8 million in USD on its bank accounts for the purpose of paying its suppliers that invoices to the Group in USD, resulting in the increase of Group's exposure to currency risk.

Price risk

The market prices for the provision of preclinical and clinical materials and services, as well as external contracted research may vary over time. The commercial prices of any of the Group's products or product candidates are currently uncertain. The Group is not exposed to commodity price risk.

Interest risk

The Group has no borrowings and is therefore not exposed to changes in the interest rates on loans and borrowings.

The Group has €98.6 million of cash on the balance sheet at December 31, 2020. The Group is implementing its treasury strategy to monitor the impact of changes in interest rates.

Credit risk

Credit risk arises from cash and other financial assets, including deposits with banks and financial institutions. Cash deposits and investments are placed only with accredited financial institutions. Credit risk is further limited by investing only in liquid instruments. The Group's maximum exposure to credit risk for the components of the statements of financial position on December 31, 2020 and 2019 are the carrying amounts as illustrated in Note 12.

There are no financial assets past due date or impaired.

Concentration of Credit Risk
Financial instruments that potentially expose the Group to concentrations of credit risk consist primarily of cash. Cash deposits are placed only with reputable financial institutions with a credit rating of not less than A- (Standard & Poor's). Credit risk is further limited by investing only in liquid instruments.

Liquidity risk

Liquidity risk is the risk that the Group might encounter difficulties in meeting the obligations associated with its financial liabilities, which are normally settled by delivering cash. The Group's approach to managing liquidity is to ensure, as far as possible, that it will always have sufficient liquidity to meet its liabilities when due.

As of December 31, 2020, the Company has cash of €98.6 million.

On February 9, 2021, the Group completed its initial public offering (IPO) with total net proceeds of $176.9 million after deducting underwriters' discount but including transaction costs.

Based on the existing operating plan, anticipated working capital requirements and available capital sources, the Company believes that it can execute on strategy and realize liquidity planning and it is able to finance its activities for at least twenty-four months following the date of these consolidated financial statements.

The Company may need additional funding in the future, which could possibly not be available to the Group at all or not at acceptable or favorable terms. This could lead to a situation where the Group would have to delay the execution of parts of its business plan.

The Group manages liquidity risks by holding appropriate reserves, taking timely action for future funding, as well as by monitoring forecasted and actual cash flows and reconciling the maturity profiles of financial assets and liabilities.

The below table summarizes the maturity profile of the Group's accrued liabilities based on contractual undiscounted payments:

	Less than 12 months	1 to 5 years	Total
December 31, 2020	€	€	€
Trade and other payables	846.952	-	846.952
Accrued liabilities	4,466,837	-	4,466,837

	Less than 12 months	1 to 5 years	Total
December 31, 2019	€	€	€
Trade and other payables	517,771	-	517,771
Accrued liabilities	1,406,359	-	1,406,359

	Less than 12 months	1 to 5 years	Total
December 31, 2018	€	€	€
Trade and other payables	246,983	-	246,983
Accrued liabilities	234,357	-	234,357

18. Share-based payments

In 2016, the Group implemented an Equity Incentive Plan (the "Plan") in order to advance the interests of the Company's shareholders by enhancing the Company's ability to attract, retain and motivate persons who are expected to make important contributions to the Company and by providing such persons with performance-based incentives that are intended to better align the interests of such persons with those of the Company's shareholders.

The main terms and conditions of the separate award agreements entered into under this Plan are provided below.

Stock Option Agreements

On March 31, 2016, the Company granted consultants an option to purchase 392,850 stock options with an exercise price of €0.01 per share with a final exercise date of March 30, 2026 unless forfeited or exercised on an earlier date. The stock options are equity-settled and may only be exercised in the event of a merger, sale or wind-up of the Company (the "Exercise Event") and certain milestones have been achieved. Further, the participant must have a specific function with the Group at the time of the Exercise Event.

On January 1, 2020 the Company has granted a total of 600,000 stock options to members of key management with an exercise price of €2.38 per share with a final exercise date of December 31, 2029 unless forfeited or exercised on an earlier date. And on February 3, 2020 a total of 308,000 stock options was granted to a member of key management with an exercise price of €2.38 per share with a final exercise date of February 2, 2030 unless forfeited or exercised on an earlier date. 25% of the aggregate number of stock options shall vest on the one-year anniversary of the grant date, and thereafter 1/48th of the aggregate number of stock options shall vest on each month until either the stock option is fully vested or the stock option holders' continuous service terminates.

On February 3, 2020 a total of 132,000 stock options was granted to a member of key management with an exercise price of €2.38 per share with a final exercise date of February 2, 2030 unless forfeited or exercised on an earlier date. Each of 2020, 2021, 2022 is a performance period. The Board of directors needs to determine the performance goals for the related performance period before September 30 of the respective year. On July 13, 2020 the performance goals for 2020 were determined and the fair value of the related stock options was reassessed for the stock options subject to the performance goals for 2020. The fair value of the stock options related to the performance periods 2021 and 2022 was reassessed on December 31, 2020. One-third of the aggregate number of stock options shall vest on the last day of each performance period if (i) the performance condition for the applicable performance period is achieved, as determined by the Board, and (ii) option holder remains in continuous service through the last day of such performance period.

On December 17, 2020 a total of 32,445 stock options were granted to employees with an exercise price of €7.25 per share with a final exercise date of September 30, 2030 unless forfeited or exercised on an earlier date. The stock options shall vest over four-year period with 25% of the stock options vesting on the one-year anniversary of the vesting commencement date and thereafter 1/48th of the aggregate number of stock options shall vest on each month until either the stock option is fully vested or the option holders' continuous service terminates. The vesting of the stock option commences on October 1, 2020.

The share-based payment expenses are recognized over the service period in the consolidated statements of profit or loss and other comprehensive income. For the years ended December 31, 2020, 2019 and 2018 an amount of €1,410,101 and €99,946 and €99,946 respectively has been recognized.

The following table illustrates the number and weighted average exercise prices of, and movements in, stock options during the year:

	2020	Weighted average exercise price	2019	Weighted average exercise price	2018	Weighted average exercise price
		€		€		€
Outstanding January 1,	392,850	0.01	392,850	0.01	392,850	0.01
Granted	1,072,445	2.53	-	-	-	-
Exercised	-	-	-	-	-	-
Forfeited	-	-	-	-	-	-
Outstanding December 31,	1,465,295	1.85	392,850	0.01	392,850	0.01

Out of the total outstanding stock options of 1,465,295 at December 31, 2020 (2019: 392,850), 194,000 stock options were vested and are exercisable (2019: none). The options outstanding at December 31, 2020 had an exercise price in the range of €0.01 to €7.25 and a weighted-average remaining contractual life of 8.0 years (2019: 6.3 years).

Restricted Award Agreement

On December 13, 2018, the Company granted 25,295 restricted stock units ("RSUs") to key management, with a purchase price of €0.01 per RSU. The RSUs shall vest upon the occurrence of an IPO or the completion of a business arrangement involving an acquisition or the option to acquire all or majority of the Company, and which arrangement is entered into as a consequence of the services rendered by the participant to the Company during the term of service or within 9 months after termination of this agreement.

On December 17, 2020 a total of 128,300 RSUs were granted to employees with a final vesting date of December 17, 2025 unless forfeited on an earlier date. The vesting of the RSUs starts at October 1, 2020. The RSUs shall vest equally over a four-year period on each of the four anniversaries of the vesting start date until either the RSUs are fully vested or the RSUs holders' continuous service terminates. In addition to the service condition, a performance condition needs to be satisfied. The performance condition shall be satisfied on the earlier to occur of the consummation of a change in control, or an IPO date, in each case, occurring prior to the five-year anniversary of the date of grant.

The fair value of €9.67 is determined based on the share value per ordinary share at the grant date, prior to applying a discount for lack of marketability.

The expenses are recognized over the service period in the consolidated statements of profit or loss and other comprehensive income. The share-based payment expense recorded for the years ended December 31, 2020 and 2019 amounted to €177,635 and €16,201, respectively.

The following table illustrates the number and weighted average purchase prices of, and movements in, RSUs during the year:

	2020	Weighted average purchase price	2019	Weighted average purchase price	2018	Weighted average purchase price
		€		€		€
Outstanding January 1,	25,295	0.01	25,295	0.01	25,295	0.01
Granted	128,300	0.00	-	-	-	-
Exercised	-	-	-	-	-	-
Forfeited	-	-	-	-	-	-
Outstanding December 31,	153,595	0.00	25,295	0.01	25,295	0.01

Fair Value Measurement of the Company's shares

The fair value of ordinary shares is determined by the Board of directors and takes into account the most recently available valuation of ordinary shares performed by an independent valuation firm and the assessment of additional objective and subjective factors we believe are relevant and which may have changed from the date of the most recent valuation through the date of the grant.

The Board of directors consider numerous objective and subjective factors to determine their best estimate of the fair value of the ordinary shares as of each grant date, including:

- The progress of the research and development programs
- Contemporaneous third-party valuations of the ordinary shares for the share issuances in 2016, 2019 and 2020
- The rights and preferences of the preferred shares relative to the ordinary shares
- The likelihood of achieving a discrete liquidity event, such as a sale of the Company or an initial public offering given prevailing market conditions
- External market and economic conditions impacting the industry sector

As Pharvaris was a private company and the equity instruments are not marketable, an Option Pricing Model ('OPM'), with estimated probabilities of two different exit scenarios (IPO and Trade Sale), was applied to back-solve the Company's total equity value such that the value per preferred B and C share is equal to the investment price per share paid in the investment round, which has been used for the fair value per ordinary share at January 1, 2020, February 3, 2020, July 13, 2020, December 17, 2020 and December 31, 2020. This estimated total equity value has been used as input to the OPM when determining the fair value of the Company's ordinary shares at the measurement dates. The OPM uses the Black-Scholes Option-Pricing Model to determine the fair value of the Company's different share classes based upon the Company's total equity value.

The inputs used in the measurement of the fair value per ordinary share at each grant/ measurement date based upon the total equity value were as follows:

	December 31, 2020	December 17, 2020	July 13, 2020	February 3, 2020	January 1, 2020
Expected volatility (%)	90%	90%	90%	80%	80%
Expected life (years)	1.6	1.6	1.6	3.0	3.0
Risk-free interest rate (%)	-0.8%	-0.8%	-0.8%	-0.6%	-0.6%
Expected dividend yield	-	-	-	-	-

The input used in the measurement of the fair value per option at each grant/measurements date using the Black-Scholes formula (including the related number of options and the fair value of the options) were as follow:

	December 31, 2020	December 17, 2020	July 13, 2020	February 3, 2020	January 1, 2020
Number of options	88,000	32,445	44,000	308,000	600,000
Fair value of the options	€6.08	€5.07	€4.74	€1.66	€1.67
Fair value of the ordinary shares	€7.25	€7.25	€5.82	€2.38	€2.38
Exercise price	€2.38	€7.25	€2.38	€2.38	€2.38
Expected volatility (%)	85%	85%	85%	85%	85%
Expected life (years)	6.1	6.1	6.0	6.1	6.1
Risk-free interest rate (%)	-0.6%	-0.7%	-0.6%	-0.6%	-0.4%
Expected dividend yield	-	-	-	-	-

Expected volatility was based on an evaluation of the historical volatilities of comparable listed biotech-companies over the most recent historical period that commensurate with the expected option life. The expected life is based on Management's best estimate of when the options will be exercised. The risk-free interest rate is based on the yield on German government Strip bonds, with tenure equal to the expected life. The expected dividend yield is zero considering the stage of the Group.

Reference is made to Note 6 for allocation of expenses in lines of the consolidated statement of income or loss and other comprehensive income.

19. Basic and diluted loss per share

Basic and diluted loss per share is calculated by dividing the loss attributable to equity holders of the Company by the weighted average number of issued and outstanding ordinary shares during the year.

The Company's potential dilutive securities have been excluded from the computation of diluted net loss per share attributable to ordinary stockholders as the effect of including them would be antidilutive.

Potentially dilutive shares that were not included in the diluted per share calculations because they would be anti-dilutive were:

	December 31, 2020	December 31, 2019	December 31, 2018
	€	€	€
Series A preferred shares	5,242,850	5,242,850	5,242,850
Series B preferred shares	7,650,147	3,003,391	-
Series C preferred shares	5,826,279	-	-

Basic and diluted loss per share

	December 31, 2020	December 31, 2019	December 31, 2018
	€	€	€
Loss attributable to equity holders of the Company	(25,985,704)	(8,027,162)	(4,313,914)
Weighted average number of ordinary shares outstanding	4,850,000	4,850,000	4,850,000
Basic and diluted loss per share	(5.36)	(1.66)	(0.89)

20. Related parties

Note 1.2 provides information about the Group's structure, including details of the subsidiaries and the holding company. The following provides the total amount of transactions that have been entered into with related parties for the relevant financial year.

Charité Research Organisation GmbH (Charité CRO)

Dr. Knolle, who has served as Chief Scientific Officer and Chief Operating Officer since its inception, is a member of the board of Charité CRO. The Company has entered into a service contract with Charité CRO according to which Charité CRO provides services supporting research for the Company. In fiscal years 2020, 2019 and 2018 payments to Charité CRO with respect to this service contract amounted to €1,025,795, €1,238,355 and €49,600, respectively.

The amount of outstanding payable was €0 at December 31, 2020 (2019: €0).

Key management personnel compensation

	2020	2019	2018
	€	€	
Short term employee benefits	1,834,423	-	-
Post employee benefits	34,934	-	-
Share-based payments	860,117	-	-
Total	2,729,474	-	-

An amount of €120,000 of the short-term employee benefits is capitalized on the consolidated statements of financial position and will be recognized in the Group's statements of profit or loss and other comprehensive income in the period between January and June 2021.

The Group engages several management entities for the purpose of providing key management services to the Group. These management entities are considered related parties, as they provide key management services and the key management personnel have key management functions within these entities. Certain key management personnel are also shareholder of the Company. The aggregate amount of expense recognized in the consolidated statements of profit or loss and other comprehensive income related to these related parties were €1,810,049 (2019 and 2018: €1,311,572 and €1,070,616). The aggregate amounts payable to the related parties were €398,489 (2019 and 2018: €55,250 and €103,777).

The below table shows in Euros the remuneration received by the individual members of the Board of Directors for the year ended December 31, 2020:

	Salary	Bonus	Pension	Consultant fee	Share based compensation	Total remuneration
Mr. Berndt Modig	404,000	132,131	12,782	63,334	147,621	759,868
	404,000	132,131	12,782	63,334	147,621	759,868

Transactions of shares in the Company

No such transactions took place in 2020 and 2019.

Options held by the Board of Directors in the Company

Share options held by the Board of Directors in the Company:

	Number of share options held as at December 31, 2020	Number of share options held as at December 31, 2019	Exercise price per share (Euros)
Mr. Berndt Modig	150,000	0	2,38

Conditions of the share options held by management are as follow:

The grant date is January 1, 2020 and the final exercise date is December 31, 2029.

Regarding the vesting dates, 1/4th of the aggregate number of Shares subject to the Option shall vest on the 12-month anniversary of the Vesting Commencement Date and 1/48th of the aggregate number of Shares subject to the Option shall vest on each subsequent monthly anniversary of the Vesting Commencement Date until either the Option is fully vested or the Option-holder's Continuous Service terminates.

21. Commitments and contingencies

This section provides additional information about items not recognized in the financial statements but could potentially have a significant impact on the Group's financial position and performance.

Non-cancellable service contracts

The group has entered into research and development commitments in relation to the developments of Group's oral bradykinin B2 receptor antagonist. The future aggregate minimum payments under these research and development commitments are as follows:

Commitment for the minimum payments in relation to the non-cancellable service contracts are payable as follows:

	2020	2019	2018
	€	€	€
Within one year	8,898,000	4,005,200	853,200
Later than one year but not later than five years	2,453,000	1,008,500	10,800
	11,351,000	5,013,700	864,000

22. Contingent liabilities and contingent assets

The Group had no contingent liabilities and no contingent assets at December 31, 2020, 2019 or 2018.

23. Events after the reporting period

On January 1, 2021, Mr. M.E. Rome resigned as member of the Board of directors. On the same date the shareholders' approved the appointment of Mr. D. Meeker and Mr. R. Glassman as members of the Board of directors and a grant of 107,000 stock options, with an exercise price of €7.25 per stock option.

On February 5, 2021, the Company's ordinary shares began trading on the Nasdaq Stock Exchange. On the same date the Company converted from a Dutch limited liability company (B.V.) to a Dutch public limited liability company (N.V.).

On February 5, 2021, a grant of 873,000 stock options was approved by the Board of directors, with an exercise price equal to the issue price of the shares.

On February 9, 2021, the Company completed its IPO. The total gross raised from the IPO were $190.2 million and the total net proceeds raised from the IPO, after deducting underwriting discounts, were $176.9 million

On May 1, 2021, Dr. R. Gaster resigned as member of the Board of directors.

On May 12, 2021, the Company announced the expansion of their leadership team through the appointment of Dr. W. Souverijns, as Chief Community Engagement & Commercial Officer.

On May 26, 2021, the Company announced that the Board has nominated Ms. V. Monges to be appointed to the Board by the General Meeting at the Company's annual general meeting 2021 contingent on her appointment by the General Meeting, Ms V. Monges will also become the Chair of the Audit Committee.

Company Financial Statements

Statement of financial position

(after appropriation of result)

	Notes	As at December 31, 2020 €	As at December 31, 2019 €
Assets			
Non-current assets			
Financial Fixed Assets			
Participation interest	1	-	-
Current assets			
Receivables	2	347,668	837,342
Other receivables and deferred expenses	3	1,256,186	40,098
Cash and cash equivalents	4	97,649,701	19,891,936
Total assets		99,253,555	20,769,376
Equity and liabilities			
Equity	5		
Share capital		235,693	130,962
Share premium		138,034,580	36,624,697
Legal reserve		(4,365)	-
Other reserves		1,979,875	392,139
Accumulated loss		(44,459,954)	(18,195,321)
Total equity		95,785,829	18,952,477
Provisions	1	1,163,594	-
Current liabilities			
Trade and other payables	6	53,757	466,271
Accrued liabilities	7	2,250,375	1,350,628
Total liabilities		3,467,726	1,816,899
Total equity and liabilities		99,253,555	20,769,376

The accompanying notes are an integral part of these financial statements

Statement of profit or loss

	Notes	2020 €	2019 €
Share in results of participating interests	1,9	(43,609,920)	-
Other income and expenses after taxes		17,345,287	(7,748,233)
Loss for the year after tax		(26,264,633)	(7,748,233)

The accompanying notes are an integral part of these financial statements

Notes to the Company financial statements

General

These company financial statements and the consolidated financial statements together constitute the statutory financial statements of Pharvaris N.V. (hereafter: 'the Company' or 'Pharvaris'). The financial information of the Company is included in the Group's consolidated financial statements, as presented on pages 140 to 168.

On September 15, 2015, Pharvaris B.V. was incorporated. Refer to note 23 of the consolidated financial statements for the disclosure on the Company's conversion from a Dutch limited liability company (B.V.) to a Dutch public limited liability company (N.V.). The description of the Company's activities and the Group structure as included in the notes to the consolidated financial statements also apply to the company financial statements.

Accounting policies

The 2020 company financial statements including the notes thereon have been prepared in accordance with Part 9 of Book 2 of the Dutch Civil Code. Section 2:362 (8) of the Dutch Civil Code, allows companies that apply IFRS as endorsed by the European Union in their consolidated financial statements to use the same measurement principles in their company financial statements. Pharvaris has prepared these company financial statements using this provision.

Since Pharvaris N.V's statement of profit or loss for 2020 is recognized in the consolidated financial statements, it is sufficient in the company financial statements to present a condensed statement of profit or loss in accordance with section 402 of Book 2 of the Dutch Civil Code.

First-time adoption of IFRS

The financial statements for the year ended December 31, 2020, are the first the Company has prepared in accordance with IFRS as adopted by the European Union (IFRS-EU). For periods up to and including the year ended December 31, 2019, the Company prepared its company financial statements in accordance with the provisions of Title 9, Book 2 of the Dutch Civil Code and the firm pronouncements in the Dutch Accounting Standards, as published by the Dutch Accounting Standards Board ('Raad voor de Jaarverslaggeving') (Dutch GAAP) as local generally accepted accounting principles.

There were no differences identified by the Company in translating its Dutch GAAP financial statements, including the statement of financial position as at 1 January 2019 and the financial statements as of, and for the year ended 31 December 2019.

The accounting policies are described in Summary of significant accounting policies of the consolidated financial statements and are deemed incorporated and repeated herein by reference.

Participating interest

The investments in participating interests are presented as financial fixed assets in the statement of financial position using the net asset value. If the Company's share of losses of subsidiaries equals or exceeds its interest in the participating interest (including related receivables, which are deemed part of the net investment), the company does not recognize any further losses, unless it has incurred legal or constructive obligations or made payments on behalf of the investment. In such case the company will recognize a provision. If the participating interest subsequently reports profits, the Company resumes recognizing its share of those profits only after its share of the profits equals the share of losses not recognized.

Share of result in participating interest

The share of result of participating interests consists of the share of the Group in the results of these participating interests.

Corporate income tax

The Company is the head of the fiscal unity including Pharvaris Holdings B.V. and Pharvaris Netherlands B.V. The Company recognizes the portion of corporate income tax charge that it would owe as an independent taxpayer, taking into account the allocation of the advantages of the fiscal unity. Deferred tax positions are recognized by the head of the fiscal unity in total. Under the standard conditions, the members of the tax group are jointly and severally liable for any corporate income taxes payable by the Company.

Presentation of company financial statements

The structure of the Company statement of financial position and Company Statement of profit or loss are aligned as much as possible with the Consolidated statements in order to achieve optimal transparency between the consolidated financial statements and the company financial statements. The Company statement of financial position has been prepared after the appropriation of results.

1. Participation interest

Movements in the participation interest were as follows:

	2020	2019
	€	€
Balance at January 1,	-	-
Additions	20,553,555	1
Net loss from participation interest	(43,609,920)	(1)
Effect of changes in foreign exchange rates	(4,365)	-
Net asset value	(23,060,730)	-
Receivable from participating interest	21,897,136	-
Provisions	1,163,594	
Closing net book amount	-	-

During 2020 the Company made a capital contribution to its participation interest of €20,553,555. The participation in Pharvaris Holdings B.V. reported a loss of €43,330,991 for the year ended December 31, 2020 (2019: €278,929). The net loss of €43,609,920 as shown in the table above represents the accumulated losses up to December 31, 2020. The participation is carried at €0, as a result of the negative equity of the participating interest.

The Company does not guarantee the liabilities of the relevant participating interest. However, the Company has concluded to have a constructive obligation to enable the participating interest to pay its liabilities, therefore, a provision for an amount of €1,163,594 is recognized in the Company statement of financial position to show the constructive obligation for the debts of its investment which reported a negative equity. Receivable from participation interests is considered to be part of the participation interests, as settlement of the receivable is neither planned nor likely to occur in the foreseeable future. Also, the Company intends to convert these outstanding balances into equity.

The Company has not recognized a provision in the 2019 financial statements, as at that time, there was no legal nor constructive obligation to enable the participating interest to pay its debts. Accordingly, the participation is carried at €0. As result of set-up of Group's corporate structure per April 1, 2020, this constructive obligation exists at December 31, 2020 and is reported prospectively.

The Company holds directly 100% of the shares of Pharvaris Holdings B.V. (2019: 100%) and holds indirectly via Pharvaris Holdings B.V. 100% of the shares of Pharvaris Netherlands B.V. (2019: 100%), 100% of the shares of Pharvaris Inc. (2019: 0%) and 100% of the shares of Pharvaris GmbH (2019: 0%).

2. Receivables

	2020	2019
	€	€
Intercompany receivables	-	650,857
VAT receivables	347,668	186,485
	347,668	837,342

Intercompany receivables relate to current account with the participating interests. The positions will be settled within one year. The receivables do not bear any interest.

3. Other receivables and deferred expenses

	2020	2019
	€	€
Prepayments	153,168	40,098
Other receivables and deferred expenses	1,103,018	-
	1,256,186	40,098

Prepayments mainly relate to prepaid insurance and research and development expenses.

Other assets mainly consist of deferred transaction costs related to in-process equity financing. The Company defers the transaction costs related to any in-process financing. Upon completion of the financing transactions, all related transaction costs are deducted from share premium.

4. Cash and cash equivalents

	2020	2019
	€	€
Cash and cash equivalents	97,649,701	19,891,936
	97,649,701	19,891,936

The Cash and cash equivalents consist of bank balances and are not subject to any restriction.

5. Equity

The capital of the Company is divided into Ordinary shares, preferred shares A, B and C, respectively. The nominal value of each share is one eurocent (€ 0.01). Preferred shares A, B and C are convertible into Ordinary shares. Total issued shares are 23,569,276 (2019: 13,096,241). All issued shares are fully paid.

	Share capital	Share premium	Legal reserve	Other reserves	Accumulated losses	**Total equity**
	€	€	€	€	€	€
Balance at January 1, 2019	100,928	15,023,205	-	275,992	(10,447,088)	4,953,037
Loss for the year, after tax	-	-	-	-	(7,748,233)	(7,748,233)
Issue of share capital	30,034	22,437,673	-	-	-	22,467,707
Transaction costs on issue of shares	-	(836,181)	-	-	-	(836,181)
Share-based payments	-	-	-	116,147	-	116,147
Balance at December 31, 2019	130,962	36,624,697	-	392,139	(18,195,321)	18,952,477
Balance at January 1, 2020	130,962	36,624,697	-	392,139	(18,195,321)	18,952,477
Loss for the year, after tax	-	-	-	-	(26,264,633)	(26,264,633)
Issue of share capital	104,731	102,410,148	-	-	-	102,514,879
Transaction costs on issue of shares	-	(1,000,265)	-	-	-	(1,000,265)
Currency translation reserve	-	-	(4,365)	-	-	(4,365)
Share-based payments	-	-	-	1,587,736	-	1,587,736
Balance at December 31, 2020	235,693	138,034,580	(4,365)	1,979,875	(44,459,954)	95,785,829

The difference between the consolidated Group equity of €18,673,548 and the Company's equity of €18,952,477 as at December 31, 2019 is the loss of €278,929 of the participation interests over the year ended December 31, 2019. Reference is made to Note 1 of these financial statements.

Legal reserve

As of December 31, 2020 the legal reserve amounted to €(4,365) (2019: €0) and relate to unrealized currency translation losses. Pursuant to Dutch law, limitations exist relating to the distribution of shareholder's equity for the entire amount of legal reserve. By their nature, unrealized losses relating to the currency translation differences reduce shareholders' equity and thereby distributable amounts.

6. Trade and other payables

	2020	2019
	€	€
Trade payables	53,757	465,643
Tax and social security liabilities	-	628
	53,757	466,271

7. Accrued liabilities

	2020	2019
	€	€
Consulting and accounting fee accruals	1,379,140	413,904
Clinical accrued liabilities	157,205	357,718
Manufacturing accrued liabilities	489,000	283,116
Pre-clinical accrued liabilities	168,000	256,850
Other accrued liabilities	57,030	39,040
	2,250,375	1,350,628

All the accrued liabilities are due within twelve months after year-end and qualify as short-term liabilities.

8. Commitments and contingencies

Non-cancellable service contracts

Commitment for the minimum payments in relation to the non-cancellable service contracts with contract research organisations are payable as follows:

	2020	2019
	€	€
Within one year	1,893,500	4,005,200
Later than one year but not later than five years	-	1,008,500
	1,893,500	5,013,700

The Company had no contingent liabilities and no contingent assets at December 31, 2020 and 2019.

Fiscal unity

The Company is the head of the fiscal unity Pharvaris N.V. in the Netherlands for income taxes and is jointly and severally liable for the income tax liabilities of the fiscal unity. Reference is made to note 10 of these financial statements.

9. Share in results of participating interests

This represents the share of the Company in the results of its participating interest of Pharvaris Holdings B.V. Reference is made to Note 1 of these financial statements.

10. Income taxes

Pharvaris N.V. is the head of the fiscal unity including Pharvaris Netherlands B.V. and Pharvaris Holdings B.V.

The fiscal unity is in a loss-making position so there was no tax charge or income recognized in the years 2020 and 2019.

The fiscal unity has tax loss carry-forwards of approximately €9.5 million (2019: €5.9 million), that are available for offsetting against future taxable profits of the companies in which the losses arose. Under Dutch tax law, for years prior to 2019, profits in a given year can be offset against tax loss carry forwards for up to nine years. In 2019, the Dutch tax law was revised to limit the carry forward period to six years.

Tax loss carry-forwards incurred in current and prior years will expire as follows:

Year	Tax losses
	€ million
2025	3.9
2026	4.4
2027	1.2
Total carry-forward losses	9.5

Deferred tax

Deferred tax assets relating to losses carried forward have not been recognized, and deferred tax assets on deductible temporary differences in excess of deferred tax liabilities on taxable temporary differences have not been recognized in the statement of profit or loss. Deferred taxes have been recognized to the extent that management concludes that there is sufficient probability as per IAS 12 that there will be future taxable profits available in the foreseeable future against which the unused tax losses can be utilized. No deferred taxes were recognized in 2019.

Movements in deferred tax balances

	R&D expenses	Other receivables	**Total**
	€	€	€
Deferred tax assets			
At January 1, 2020	-	-	-
(Charged)/credited			
- Profit or loss	1,964,583	-	1,964,583
At December 31, 2020	1,964,583	-	1,964,583
Deferred tax liability			
At January 1, 2020	-	-	-
(Charged)/credited			
- Profit or loss	-	(1,964,583)	**(1,964,583)**
At December 31, 2020	-	(1,964,583)	**(1,964,583)**
Net deferred tax assets at December 31,2020			-

The total unrecognized deferred tax assets from temporary differences amounts to €0.9 million (2019: €2.9 million).

11. Related parties

Note 1.2 provides information about the Group's structure, including details of the subsidiaries and the holding company and the total amount of transactions that have been entered into with related parties for the relevant financial year. Reference is made to Note 20 of the consolidated financial statements.

Charité Research Organisation GmbH (Charité CRO)

Dr. Knolle, who has served as Chief Scientific Officer and Chief Operating Officer since its inception, is a member of the board of Charité CRO. The Company has entered into a service contract with Charité CRO according to which Charité CRO provides services supporting research for the Company. In fiscal years 2020 and 2019 payments to Charité CRO with respect to this service contract amounted to €1,025,795, €1,238,355 and €49,600, respectively.

The amount of outstanding payable was €0 at December 31, 2020 (2019: €0).

12. Remuneration of the board of Directors

The emoluments, including pension costs as referred to in Section 2:383(1) of the Netherlands Civil Code, charged in the financial year to the Company and group companies by the Board of Directors members amounts to €759,868 (2019: €283,300). Further reference is made to note 20 of the consolidated financial statements.

13. Employee benefits and information

The Company had no employees during the fiscal year (2019: nil).

Total costs related to share-based payments for the amount of €1,587,736 (2019: €116,147) are included in the company financial statements. Reference is made to note 18 in the consolidated financial statements for disclosure on the share-based payments.

14. Auditor's fee

The following fees were charged by PwC Accountants N.V. to the Company and its subsidiaries, as referred to in Section 2:382a(1) and (2) of the Netherlands Civil Code. The costs are allocated to the year which the services are related to.

	PwC Accountants N.V.	
	2020	2019
	€	€
Audit of financial statements	366,000	119,000
Other assurance services	278,000	-
Total	644,000	119,000

15. Events after the reporting period

Reference is made to Note 23 in the consolidated financial statements.

Signature page to the Pharvaris N.V. 2020 financial statements

Leiden, May 31, 2021

_____	_____
B.A.E. Modig	M. Kleijwegt
_____	_____
R.P.L. Droller	R.H. Glassman
_____	_____
J.G.C.P. Schikan	D.P. Meeker

OTHER INFORMATION

Independent auditor's report

The independent auditor’s report is included in the next page.

Profit appropriation provisions

Pursuant to the Company's articles of association as they current read, any profits of the Company shall be appropriated as follows, and in the following order of priority:

a. to the extent that any preferred shares have been cancelled without full repayment as described in the articles of association and without such deficit subsequently having been paid in full, an amount equal to any such (remaining) deficit shall first be distributed to those who held those preferred shares at the moment of such cancellation becoming effective;

b. if preferred shares are issued and outstanding and to the extent that the mandatory annual distribution on the preferred shares (i.e., an amount equal to the applicable interest rate calculated over the aggregate amount paid up on those preferred shares, calculated in accordance with the relevant provisions of the articles of association), or part thereof, in relation to previous financial years has not yet been paid in full, an amount equal to any such (remaining) deficit shall be distributed on the preferred shares;

c. if preferred shares are issued and outstanding, the mandatory annual distribution (as described above under b.) payable on preferred shares shall then be distributed on the preferred shares;

d. following those distributions, the Board shall determine which part of the remaining profits shall be added to the Company's reserves; and

e. subject to a proposal by the Board to that effect, the remaining profits shall be at the disposal of the General Meeting for distribution on the ordinary shares.

Shares carrying limited economic entitlement

There are currently no outstanding shares which carry a limited entitlement to the profits or reserves in the Company.

Branches

The Company has no branch offices.

Independent auditor's report

To: the general meeting of Pharvaris N.V.

Report on the financial statements 2020

Our opinion

In our opinion:

- the consolidated financial statements of Pharvaris N.V. (formerly Pharvaris B.V.) together with its subsidiaries ('the Group') give a true and fair view of the financial position of the Group as at 31 December 2020 and of its result and cash flows for the year then ended in accordance with International Financial Reporting Standards as adopted by the European Union ('EU-IFRS') and with Part 9 of Book 2 of the Dutch Civil Code;
- the company financial statements of Pharvaris N.V. ('the Company') give a true and fair view of the financial position of the Company as at 31 December 2020 and of its result for the year then ended in accordance with Part 9 of Book 2 of the Dutch Civil Code.

What we have audited

We have audited the accompanying financial statements 2020 of Pharvaris N.V., Leiden. The financial statements include the consolidated financial statements of the Group and the company financial statements.

The consolidated financial statements comprise:

- the consolidated statement of financial position as at 31 December 2020;
- the following statements for 2020: the consolidated statements of profit or loss and other comprehensive income, changes in equity and cash flows; and
- the notes, comprising significant accounting policies and other explanatory information.

The company financial statements comprise:

- the company statement of financial position as at 31 December 2020;
- the company statement of profit or loss for the year then ended;
- the notes, comprising the accounting policies applied and other explanatory information.

The financial reporting framework applied in the preparation of the financial statements is EU-IFRS and the relevant provisions of Part 9 of Book 2 of the Dutch Civil Code for the consolidated financial statements and Part 9 of Book 2 of the Dutch Civil Code for the company financial statements.

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The basis for our opinion

We conducted our audit in accordance with Dutch law, including the Dutch Standards on Auditing. We have further described our responsibilities under those standards in the section 'Our responsibilities for the audit of the financial statements' of our report.

We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our opinion.

Independence

We are independent of Pharvaris N.V. in accordance with the 'Wet toezicht accountantsorganisaties' (Wta, Audit firms supervision act), the 'Verordening inzake de onafhankelijkheid van accountants bij assuranceopdrachten' (ViO, Code of Ethics for Professional Accountants, a regulation with respect to independence) and other relevant independence regulations in the Netherlands. Furthermore, we have complied with the 'Verordening gedrags- en beroepsregels accountants' (VGBA, Dutch Code of Ethics).

Our audit approach

Overview and context

Pharvaris N.V. is a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapies for rare diseases with significant unmet need, initially focused on angioedema and other bradykinin-mediated diseases. Pharvaris N.V. was incorporated on 30 September 2015 and is headquartered in Leiden, the Netherlands. We considered our group audit scope and approach as set out in the section 'The scope of our group audit'. The Company incurred significant operating losses and has not generated revenues. The Company entered into financing agreements by issuing Series B and Series C preferred shares, has initiated the process of listing its ordinary shares on the Nasdaq stock market, so has incurred transaction costs in 2020. Also, the Company monitored the developments surrounding the COVID-19 pandemic and has taken steps to identify and mitigate the adverse effects and risks to the Company as a result of the pandemic. We paid specific attention to the areas of focus driven by the operations of the Group, as set out below.

The Company's focus on the clinical development and the research and development efforts relating to the development of their product candidates characterised the financial year 2020. In addition, the Company invested in the development of their internal organisation and management functions.

As part of designing our audit, we determined materiality and assessed the risks of material misstatement in the financial statements. In particular, we considered where management made important judgements, for example, in respect of significant accounting estimates that involved making assumptions and considering future events that are inherently uncertain. In note 2.18 of the consolidated financial statements, the Company describes the areas of judgement in applying accounting policies and the key sources of estimation uncertainty. Of these areas, we considered the share-based payments as a key audit matter given the complexity, subjectivity and significant estimation uncertainty and the related higher inherent risks of material misstatement in determining the fair value of the share-based payments, as set out in the section 'Key audit matters' of this report.

Other areas of focus, that have not been considered as key audit matters, were the accounting of transaction costs related to the financing activities and the in-process equity financing, and the impact of COVID-19 on the Company's financial condition or liquidity of the Company.

As in all our audits, we also addressed the risk of management override of controls, including evaluating whether there was evidence of bias by management that may represent a risk of material misstatement due to fraud.

We ensured that the audit team included the appropriate skills and competences which are needed for the audit of a clinical stage biopharmaceutical company. We therefore included experts and specialists in the areas of share-based payments and valuations in our team.

The outline of our audit approach was as follows:

Materiality

- Overall materiality: €241,000.

Audit scope

- Due to the COVID-19 pandemic, we refrained from any activities on site. For the exchange of data, a data-exchange platform provided by us as well as emails were used. Interviews and meetings were conducted virtually.
- We performed all the audit procedures for the audit of the group and company financial statements as the financial reporting and accounting functions for all entities in the Group are located, operated and managed centrally in Leiden.
- Audit coverage: 100% of consolidated total assets, 100% of total expenses and 100% of consolidated loss before tax.

Key audit matters

- Share-based payments

Materiality

The scope of our audit is influenced by the application of materiality, which is further explained in the section 'Our responsibilities for the audit of the financial statements'.

Based on our professional judgement we determined certain quantitative thresholds for materiality, including the overall materiality for the financial statements as a whole as set out in the table on the next page. These, together with qualitative considerations, helped us to determine the nature, timing and extent of our audit procedures on the individual financial statement line items and disclosures and to evaluate the effect of identified misstatements, both individually and in aggregate, on the financial statements as a whole and on our opinion.

Overall group materiality	€241,000 (2019: €200,000).
Basis for determining materiality	We used our professional judgement to determine overall materiality. As a basis for our judgement we used 1% of total expenses.
Rationale for benchmark applied	We used total expenses as the primary benchmark, a generally accepted auditing practice, based on our analysis of the common information needs of users of the financial statements. On this basis, we believe that the total expenses are an important metric for the financial performance of the Company. This is a change from 2019, when we used 1% of total assets, as a basis for determining materiality given that the Company was in an early start-up phase with a stakeholders' focus on the availability of funds to continue to finance research and development activities and operating costs.

We also take misstatements and/or possible misstatements into account that, in our judgement, are material for qualitative reasons.

We agreed with the board of directors that we would report to them misstatements identified during our audit above €12,000 (2019: €10,000) as well as misstatements below that amount that, in our view, warranted reporting for qualitative reasons.

The scope of our group audit

Pharvaris N.V. is the parent company of a group of entities. The financial information of this group is included in the consolidated financial statements of Pharvaris N.V.

We tailored the scope of our audit to ensure that we, in aggregate, provide sufficient coverage of the financial statements for us to be able to give an opinion on the financial statements as a whole, taking into account the management structure of the Group, the nature of operations of its components, the accounting processes and controls, and the markets in which the components of the Group operate. In establishing the overall group audit strategy and plan, we determined that the group engagement team performs all the audit procedures for the audit of the Group and company financial statements as the financial reporting and accounting functions for all entities in the Group are located, operated and managed centrally in Leiden.

In total, in performing these procedures, we achieved the following coverage on the financial line items:

Total assets	100%
Total expenses	100%
Profit before tax	100%

Due to the COVID-19 pandemic, we refrained from any activities on site. For the exchange of data, a date-exchange platform provided by us as well as emails were used. Interviews and meetings were conducted virtually. We have ensured we have performed the appropriate procedures and obtained sufficient appropriate audit evidence to support our opinion. By performing the procedures above, we have been able to obtain sufficient and appropriate audit evidence on the Group's financial information, as a whole, to provide a basis for our opinion on the financial statements.

Our focus on the risk of fraud

Our objectives

The objectives of our audit are:

In respect to fraud:

- to identify and assess the risks of material misstatement of the financial statements due to fraud;
- to obtain sufficient appropriate audit evidence regarding the assessed risks of material misstatement due to fraud, through designing and implementing appropriate audit responses; and
- to respond appropriately to fraud or suspected fraud identified during the audit.

The primary responsibility for the prevention and detection of fraud lies with the board of directors. We refer to section 3 of the annual report where the board of directors included their fraud risk assessment.

Our risk assessment

As part of our process of identifying fraud risks, we evaluated fraud risk factors with respect to financial reporting fraud, misappropriation of assets and bribery and corruption, particularly in light of the material weaknesses in internal control. We evaluated the fraud risk factors to consider whether those factors indicated a risk of material misstatement due to fraud.

As in all of our audits, we addressed the risk of management override of internal controls, including evaluating whether there was evidence of bias by management that may represent a risk of material misstatement due to fraud. We refer to the key audit matter on share-based payments, that is an example of our approach related to an area of higher risk due to accounting estimates where management makes significant judgments.

Our response to the risks identified

We performed the following audit procedures to respond to the assessed risks:

- We evaluated the design and the implementation of internal controls that mitigate fraud risks.
- We performed testing of high-risk journal entries and evaluated key estimates and judgements for bias by Pharvaris N.V. Where we identified instances of unexpected journal entries or other risks through our journal entry testing procedures, we performed additional audit procedures to address each identified risk. These procedures also included testing of transactions back to source information.
- With respect to the risk of misappropriation of assets, and in view of the material weaknesses in internal control, we performed substantive testing of payments to identify any unauthorized or fraudulent payments. No such unauthorized or fraudulent payments were noted.
- We incorporated elements of unpredictability in our audit.
- We considered the outcome of our other audit procedures and evaluated whether any findings or misstatements were indicative of fraud. If so, we re-evaluated our assessment of fraud risk and its resulting impact on our audit procedures.

Key audit matters

Key audit matters are those matters that, in our professional judgement, were of most significance in the audit of the financial statements. We have communicated the key audit matters to the board of directors. The key audit matters are not a comprehensive reflection of all matters identified by our audit and that we discussed. In this section, we described the key audit matters and included a summary of the audit procedures we performed on those matters.

We addressed the key audit matters in the context of our audit of the financial statements as a whole, and in forming our opinion thereon. We do not provide separate opinions on these matters or on specific elements of the financial statements. Any comment or observation we made on the results of our procedures should be read in this context.

Key audit matter	***Our audit work and observations***
Share-based payments *Note 18 in the consolidated financial statements* Total share-based compensation expenses for the year 2020 amount to €1.6 million (Research and development €1.2 million & general and administrative expenses €0.4 million). During the year, certain key management and employees were granted stock options under the 2016 Equity Incentive Plan with either a service requirement ('Service Options') and/or service and performance requirement ('Performance Options'). In addition, certain employees were granted restricted stock units (RSUs) during 2020. As Pharvaris N.V. was a private company and the equity instruments are not marketable, an Option Pricing Model ('OPM'), with estimated probabilities of two different exit scenarios (IPO and Trade Sale), was applied to estimate the Company's implied total equity value such that the value per Preferred B and Preferred C share is equal to the investment price per share paid in the respective investment round, which was then used to determine the fair value per ordinary share at the grant or measurement dates. This estimated total equity value has been used as input to the OPM when determining the fair value of the Company's ordinary shares at the measurement dates. The OPM uses the Black-Scholes Option-Pricing Model to determine the fair value of the Company's different share classes based upon the Company's total equity value. In addition, the Company used the Black-Scholes formula in the measurement of the fair value per stock option at each grant/measurement date.	We obtained the relevant contracts and grant letters and gained a detailed understanding of the arrangements based on these underlying documents. Additionally, we obtained and assessed the related supporting documentation, such as the plan terms and conditions of the options, the valuation prepared by the third-party valuation specialist hired by the Company, and the Black-Scholes pricing model, including valuation inputs such as exercise price, fair value of the ordinary shares, volatility, risk free rate and dividend yield. Together with our valuation experts, we evaluated the analysis performed and challenged the key assumptions used by management and their third-party valuation specialist in determining the fair value of the underlying shares. We performed the following procedures: • reconciled the exercise price and the number of options and RSUs granted to the grant letters and/or board resolutions; • reconciled the fair value of ordinary shares against fair value determined by the third-party valuation specialist; • assessed the expected volatility against observable historical volatilities of peer group companies; • tested the risk free rate as derived based on German government Strip bonds as of the grant date by comparing to relevant market data; • evaluated management's assumptions in determining the expected option life and dividend yield; • evaluated the OPM methodology and the estimated probabilities of the two different exit scenarios;

Key audit matter	*Our audit work and observations*
In view of the complexity, subjectivity and significant estimation uncertainty and the related higher inherent risks of material misstatement in determining the fair value of the share-based payments, we determined that this is a key audit matter.	• recalculated the implied total equity value of the Company and the values of the ordinary shares, the stock options and the RSUs to determine that these are within an acceptable range; and, • agreed the calculations and the key assumptions to supporting documentation and the financial statement disclosures. Furthermore, we assessed the independence, competence and objectivity of the third-party valuation specialist. Finally, we evaluated whether the disclosures in respect of the share based payments were adequate. Our audit procedures outlined above, did not result in any remaining material findings.

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Report on the other information included in the annual accounts

In addition to the financial statements and our auditor's report thereon, the annual accounts contains other information that consists of:

- the Board Report;
- the other information pursuant to Part 9 of Book 2 of the Dutch Civil Code.

Based on the procedures performed as set out below, we conclude that the other information:

- is consistent with the financial statements and does not contain material misstatements;
- contains the information that is required by Part 9 of Book 2 of the Dutch Civil Code.

We have read the other information. Based on our knowledge and understanding obtained in our audit of the financial statements or otherwise, we have considered whether the other information contains material misstatements.

By performing our procedures, we comply with the requirements of Part 9 of Book 2 of the Dutch Civil Code and the Dutch Standard 720. The scope of such procedures was substantially less than the scope of those performed in our audit of the financial statements.

The board of directors is responsible for the preparation of the other information, including the Board Report and the other information in accordance with Part 9 of Book 2 of the Dutch Civil Code.

Report on other legal and regulatory requirements

Our appointment

We were appointed as auditors of Pharvaris N.V. following the passing of a resolution by the shareholders at the annual meeting held on 2 June 2020. Our appointment has been renewed annually by shareholders representing a total period of uninterrupted engagement appointment of 1 year.

Responsibilities for the financial statements and the audit

Responsibilities of the board of directors

The board of directors is responsible for:

- the preparation and fair presentation of the financial statements in accordance with EU-IFRS and with Part 9 of Book 2 of the Dutch Civil Code; and for
- such internal control as the board of directors determines is necessary to enable the preparation of the financial statements that are free from material misstatement, whether due to fraud or error.

As part of the preparation of the financial statements, the board of directors is responsible for assessing the Company's ability to continue as a going concern. Based on the financial reporting frameworks mentioned, the board of directors should prepare the financial statements using the going concern basis of accounting unless the board of directors either intends to liquidate the Company or to cease operations, or has no realistic alternative but to do so. The board of directors should disclose events and circumstances that may cast significant doubt on the Company's ability to continue as a going concern in the financial statements.

Our responsibilities for the audit of the financial statements

Our responsibility is to plan and perform an audit engagement in a manner that allows us to obtain sufficient and appropriate audit evidence to provide a basis for our opinion. Our objectives are to obtain reasonable assurance about whether the financial statements as a whole are free from material misstatement, whether due to fraud or error and to issue an auditor's report that includes our opinion. Reasonable assurance is a high but not absolute level of assurance, which makes it possible that we may not detect all material misstatements. Misstatements may arise due to fraud or error. They are considered to be material if, individually or in the aggregate, they could reasonably be expected to influence the economic decisions of users taken on the basis of the financial statements.

Materiality affects the nature, timing and extent of our audit procedures and the evaluation of the effect of identified misstatements on our opinion.

A more detailed description of our responsibilities is set out in the appendix to our report.

Eindhoven, 10 June 2021
PricewaterhouseCoopers Accountants N.V.

Original has been signed by R.M.N. Admiraal RA

Appendix to our auditor's report on the financial statements 2020 of Pharvaris N.V.

In addition to what is included in our auditor's report, we have further set out in this appendix our responsibilities for the audit of the financial statements and explained what an audit involves.

The auditor's responsibilities for the audit of the financial statements

We have exercised professional judgement and have maintained professional scepticism throughout the audit in accordance with Dutch Standards on Auditing, ethical requirements and independence requirements. Our audit consisted, among other things of the following:

- Identifying and assessing the risks of material misstatement of the financial statements, whether due to fraud or error, designing and performing audit procedures responsive to those risks, and obtaining audit evidence that is sufficient and appropriate to provide a basis for our opinion. The risk of not detecting a material misstatement resulting from fraud is higher than for one resulting from error, as fraud may involve collusion, forgery, intentional omissions, misrepresentations, or the intentional override of internal control.
- Obtaining an understanding of internal control relevant to the audit in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control.
- Evaluating the appropriateness of accounting policies used and the reasonableness of accounting estimates and related disclosures made by the board of directors.
- Concluding on the appropriateness of the board of directors' use of the going concern basis of accounting, and based on the audit evidence obtained, concluding whether a material uncertainty exists related to events and/or conditions that may cast significant doubt on the Company's ability to continue as a going concern. If we conclude that a material uncertainty exists, we are required to draw attention in our auditor's report to the related disclosures in the financial statements or, if such disclosures are inadequate, to modify our opinion. Our conclusions are based on the audit evidence obtained up to the date of our auditor's report and are made in the context of our opinion on the financial statements as a whole. However, future events or conditions may cause the Company to cease to continue as a going concern.
- Evaluating the overall presentation, structure and content of the financial statements, including the disclosures, and evaluating whether the financial statements represent the underlying transactions and events in a manner that achieves fair presentation.

Considering our ultimate responsibility for the opinion on the consolidated financial statements, we are responsible for the direction, supervision and performance of the group audit. In this context, we have determined the nature and extent of the audit procedures for components of the Group to ensure that we performed enough work to be able to give an opinion on the financial statements as a whole. Determining factors are the geographic structure of the Group, the significance and/or risk profile of group entities or activities, the accounting processes and controls, and the industry in which the Group operates. On this basis, we selected group entities for which an audit or review of financial information or specific balances was considered necessary.

We communicate with the board of directors regarding, among other matters, the planned scope and timing of the audit and significant audit findings, including any significant deficiencies in internal control that we identify during our audit.

We provide the board of directors with a statement that we have complied with relevant ethical requirements regarding independence, and to communicate with them all relationships and other matters that may reasonably be thought to bear on our independence, and where applicable, related actions taken to eliminate threats or safeguards applied.

From the matters communicated with the board of directors, we determine those matters that were of most significance in the audit of the financial statements of the current period and are therefore the key audit matters. We describe these matters in our auditor's report unless law or regulation precludes public disclosure about the matter or when, in extremely rare circumstances, not communicating the matter is in the public interest.