Risk Factors

An investment in Santhera shares ("Shares") involves a high degree of risk. Prospective investors should carefully consider the risks related to any investment in the Shares before making a decision to invest in the Shares. The risks described below are not the only ones applicable to Santhera Pharmaceuticals Holding AG (the "Company") and/or its subsidiaries (together with the Company, the "Group", "Santhera", "we" or "us"). Additional risks not presently known or currently deemed immaterial may also impair the Group's business, results of operations, financial condition or prospects. The realization of one or more of these risks individually or together with other circumstances may have a material adverse effect on the Group's business, results of operations, financial condition or prospects. In addition, each of the risks set out below could adversely affect the trading price of the Shares, and investors in Shares may lose all or a part of their investment.

The order in which the risks are presented below is not intended to indicate the probability of their occurrence or the materiality of the risk.

By issuing these risk factors, we do not promote or solicit any investment in the Shares or related securities.

Date: December 12, 2018

A. Risks related to our business and financial situation

1. Risks related to our financial position, capital needs and transactions

(1) We are an early stage pharmaceutical company and have only one marketed product, Raxone® for the treatment of Leber's hereditary optic neuropathy (LHON), which constitutes a relatively small business opportunity. In addition, we have one late-stage product candidate, Raxone® for the treatment of Duchenne Muscular Dystrophy (DMD), for which our recent applications for market authorization in the EU have been unsuccessful and for which we have not received marketing authorization for any country, as well as two early stage product candidates. We have incurred significant losses since our inception and expect to incur substantial losses and negative operating cash flows for the foreseeable future and may never achieve or maintain profitability.

We are an early stage pharmaceutical company. We currently have no products approved for commercial sale other than Raxone®, for which we received marketing authorization in the European Union (the European Union or the European Economic Area, as applicable, the "**EU**") in September 2015 for the treatment of Leber's hereditary optic neuropathy ("**LHON**"), whose market is, however, small. We filed a marketing authorization application ("**MAA**") with the European Medicines Agency ("**EMA**") with respect to Raxone® for the treatment of DMD in certain patients with declining respiratory function who are currently not taking steroids, which is an indication with respect to which we believe the potential market may be substantially larger than that for the treatment of LHON due to the larger number of patients affected by this condition. However, in September 2017, the EMA's Committee for Medicinal Products for Human Use ("**CHMP**") issued a negative opinion on our MAA, and in January 2018, the CHMP maintained such negative opinion following a re-examination procedure that we requested and despite an updated proposal for post-authorization measures and a clarification of the wording of the indication that we had proposed.

We have incurred consistent cash-outflow and significant losses since our inception, including a net loss of CHF 21.2 million in 2015 (excluding the one-time effect of a reversal of an impairment), of CHF 35.4 million in 2016, of CHF 51.5 million in 2017 and of CHF 39.9 million in the nine months ended September

30, 2018. We expect to continue to incur significant operating losses for the foreseeable future, as we continue our development and commercialization efforts and make investments. We expect our expenses to increase substantially over the coming years, primarily due to higher operating expenses in connection with our ongoing development activities as well as the ramping up of our commercialization activities relating to Raxone®. To become and remain profitable, we must successfully complete the development of our product candidates, obtain marketing authorizations and pricing and reimbursement approvals for them, expand our product pipeline, maintain and manage our manufacturing arrangements with third parties, maintain and build up an effective internal sales and marketing organization, establish and maintain sales and marketing arrangements with third parties and raise sufficient funds to finance our activities. We may never succeed in these activities, and even if we do, we may never generate sales that are significant enough to achieve profitability.

(2) We may need to obtain substantial additional funding for purposes of our continuing operations and capital expenditures. We may not be able to obtain future financing or only obtain it on terms that significantly dilute the Company's shareholders and/or restrict our flexibility to operate. A material uncertainty exists as to whether the Company's current funding is sufficient to support its going concern for another twelve months.

As at September 30, 2018, we had cash and cash equivalents of CHF 19.7 million, excluding restricted cash we placed in escrow for interest payments during the first three years of the term of our CHF 60 million Senior Unsecured Convertible Bonds 2017-2022 (the "**Bonds**"). Sales in the first nine months of 2018 were CHF 23.6 million and we incurred a net loss for that period of CHF 39.9 million. Our operations have used substantial amounts of cash since our inception and we continue to require significant amounts of cash for operating our business and to satisfy our obligations. We also expect our expenses to increase further in connection with our ongoing development activities as well as the ramping up of our commercialization activities relating to Raxone®.

We may need to obtain substantial additional funds for purposes of our continuing operations and capital expenditures. Without such funds, there will be material uncertainty as to whether we will be able to continue as a going concern for another twelve months.

We depend significantly on external equity and debt financing, in addition to cash flows we generate from ongoing product sales and potential milestone payments. Such financing may not be available to us on acceptable terms, or at all, in particular in the short term. Also, the Bonds prohibit us from issuing any secured marketable debt instruments or incurring any secured financial debt (including bank debt) exceeding CHF 10.0 million in the aggregate (subject to exceptions) unless the Bonds are secured equally and rateably, or the Paying and Conversion Agent under the Bonds consents, which could adversely impact our ability to raise additional debt financing. If we fail to obtain additional funds on acceptable terms when needed, we may have to delay, reduce or terminate our product development programs or the production and commercialization of Raxone®, we may not be able to meet the cash requirements for operating our business and making payments with respect to our financial obligations, including interest and principal payments on our Bonds, and we may be required to file for bankruptcy.

If we are able to raise additional equity or issue equity-linked instruments, the Company's shareholders could be significantly diluted. If we incur additional debt, the terms of such debt may subject us to restrictive covenants or security obligations that limit our flexibility in conducting future business activities, such as incurring additional debt or acquiring or licensing intellectual property rights.

(3) Our marketed product, Raxone® in LHON, will not allow us to become profitable. Our future profitability, if any, will depend on us being able to obtain marketing authorization and, thereafter, pricing and reimbursement approvals for our product candidates, in particular Raxone® in DMD, as well as potentially in other indications.

In 2017, we generated net sales of CHF 22.9 million with Raxone® in LHON, our only marketed product. Even if we reach the peak sales potential of Raxone® in LHON, this product alone will not allow us to become profitable. If Raxone® in LHON remains our only marketed product, we will not be able to become profitable and may eventually have to shut down our operations.

Our future success and profitability (if any) will depend on our ability to obtain marketing authorization and, thereafter, pricing and reimbursement approvals for Raxone® in DMD in the EU and in the United States of America (the "**U.S.**"), as well as on other factors. We may never receive a marketing authorization for Raxone® in DMD. Even if we eventually obtain such marketing authorization for the EU, we may not receive it on terms acceptable to us, or our product may not be commercially viable. Moreover, pricing and reimbursement decisions in the EU remain a competence of each Member State and therefore may vary significantly from one country to another.

We have unsuccessfully applied for marking authorization for Raxone® in DMD patients with declining respiratory function who are currently not taking steroids, and have not yet sought marketing authorization for Raxone® in DMD patients who are receiving steroids, and our phase III clinical trial ("**SIDEROS**") for Raxone® in this subgroup of DMD patients is still ongoing and its outcome is uncertain. We have not filed a New Drug Application ("**NDA**") for Raxone® in DMD in the U.S., and there is considerable uncertainty around whether the U.S. Food & Drug Administration (the "**FDA**") would accept an NDA filing based on the limited data from our phase III clinical trial of Raxone® in certain DMD patients with declining respiratory function who were not receiving steroids ("**DELOS**"). Even if the FDA accepts an NDA filing on this basis and grants the respective marketing authorization, a subsequent negative outcome of the SIDEROS trial could potentially jeopardize the maintenance of such marketing authorization.

If we are unsuccessful or significantly delayed in obtaining marketing authorization for Raxone® in DMD or its subsequent commercialization, or in the further commercialization of Raxone® in LHON, we would have to rely on the further development of vamorolone in DMD, for which we have acquired an option to in-license, our early stage pipeline that comprises omigapil in congenital muscular dystrophy ("**CMD**") (currently in phase I clinical trial) and our recently in-licensed compound POL6014 in cystic fibrosis ("**CF**") (currently in phase I clinical trial). Given the uncertainties around the development and commercialization of pharmaceuticals, we may not be able to develop and commercialize any such product candidates in a timely manner or at all.

(4) We may never receive a marketing authorization for Raxone® in DMD.

The CHMP has issued a negative opinion on our MAA for Raxone® in certain DMD patients even after re-examination. We may fail to collect further evidence to strengthen the clinical data package for Raxone in preparation of a refiling of an MAA with the EMA, and even if we are able to collect such additional data, we may not be able to make an improved case and there is a material risk that we cannot refile an MAA with the EMA. Even if we refile an MAA with the EMA, the CHMP may consider the additional data submitted by us not to be compelling enough to support a positive opinion by it and may issue a negative opinion on such MAA. Also, regulators elsewhere, in particular the FDA, if and when we file an NDA for Raxone® in DMD in the U.S., may be more reluctant to grant us marketing authorization for Raxone® in DMD given the negative opinion by the CHMP. If we do not receive a marketing authorization for Raxone® in DMD, we might have to abandon our development activities with regard to Raxone® in indications other than LHON.

(5) News on our development and commercialization efforts that we expect to receive during the coming months and in the longer term may have a significant and potentially adverse effect on the value of the Group and, as a consequence, the market price of the Shares.

The value of the Group strongly depends on the results of our clinical trials and on the decisions by regulatory authorities. We expect to receive material new information on such matters in the coming months and in the longer term. In particular, depending on the outcome of discussions currently held with clinical experts and regulators, we may or may not be in a position to further develop omigapil in CMD. Moreover, we currently expect top line data of our phase III clinical trial of Raxone® in certain DMD patients with declining respiratory function who are receiving steroids (SIDEROS) in 2020. Such news or its delay may have a significant adverse effect on the value of the Group and adversely affect its business and prospects. As a consequence, the market price of the Shares is expected to be volatile. Should any such news be unfavorable, the market price of the Shares may significantly decline and, potentially, not recover.

(6) We may not realize the benefits of our recent in-licensing of POL6014 from Polyphor Ltd ("Polyphor"), of our recent option to in-license vamorolone from Idorsia Pharmaceuticals Ltd ("Idorsia"), of any other product candidates or compounds that we may in-license or acquire, of any strategic alliances that we may form, joint ventures that we may create, or strategic transactions that we may enter into in the future.

We have acquired, in-licensed or acquired an option to in-license all of our current product candidates, typically against payment of upfront consideration and milestone and royalty payments. In February 2018, we in-licensed the compound POL6014 from Polyphor against an initial consideration (paid in Shares) of CHF 6.5 million, and we agreed to cash payments of up to CHF 121 million contingent on future development, regulatory and particularly sales milestones. In November 2018, we entered into the Option Agreement with Idorsia, under which we have acquired an option to obtain from Idorsia an exclusive sub-license to commercialize ReveraGen BioPharma, Inc.'s ("**ReveraGen**") vamorolone, a non-hormonal steroid modulator developed by ReveraGen. As consideration for the acquisition of the option for the exclusive sub-license relating to ReveraGen's vamorolone, we paid Idorsia an equity consideration of 1,000,000 Shares and have agreed to pay Idorsia a cash consideration in the amount of USD 20.0 million. Under the Option Agreement, Idorsia will be entitled to receive a cash payment from us of USD 30.0 million upon exercise of the option and commercial milestone payments of up to USD 80 million in the DMD indication and four one-time sales milestone payments of up to USD 130 million in aggregate. Regulatory milestone payments payable by the Company to Idorsia for three additional indications amount to up to USD 205 million in aggregate. Upon commercialization of vamorolone, the Company has committed to pay to Idorsia tiered royalties ranging from a single-digit to low double-digit percentage on the annual net sales of vamorolone. Further to vamorolone, we are currently evaluating several additional potential in-licensing and acquisition opportunities in our three therapeutic areas. We may not be able to realize the benefit of our past or future acquisitions or in-licensing transactions, or they may turn out to have been made at too high a price. Likewise, any strategic alliances, joint ventures or strategic transactions that we may enter into in the future may fail to achieve the expected results and may divert capital resources and management time. It is unclear whether and when any product candidates may generate revenues for the Company.

2. Risks related to the development of our product candidates

(1) Any setbacks impacting our only lead compound, idebenone (the active ingredient in Raxone®), may adversely affect our only marketed product and our only late-stage product candidate simultaneously.

We rely on one lead compound, idebenone, for use in our marketed product, Raxone® in LHON and our late-stage product candidate, Raxone® in DMD. In aggregate, we rely on only three compounds (including idebenone) in our current development and commercialization efforts, and both our clinical development of omigapil in CMD and the development of POL6014 in CF are in early clinical stages (phase I clinical trial). Any adverse effects resulting from the use of idebenone in the human body, or any difficulty in the manufacture, or problem with the supply, of idebenone, or any measures taken by regulators in relation to idebenone, could adversely affect our marketed product and our late-stage product candidate simultaneously.

(2) Our product candidates must prove their efficacy and safety in rigorous clinical testing. Drug development involves a lengthy and expensive process, with an uncertain outcome. Failure may occur at any stage of clinical development.

Before we may seek marketing authorization for any product candidate, we must conduct extensive clinical trials to demonstrate its safety and efficacy in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is inherently uncertain as to its outcome. A failure of one or more clinical trials can occur at any stage of testing. Promising results in preclinical studies of a product candidate may not be predictive of similar results in humans during clinical trials, and successful results from early clinical trials may not be replicated in later and larger clinical trials or in clinical trials for different indications or different patient populations. For example, the results of our phase III clinical trial (DELOS) of Raxone® in certain DMD patients are not predictive of the results of our ongoing phase III clinical trial (SIDEROS) of Raxone® in a different DMD patient population; and the full results of our phase I clinical trial (CALLISTO) of omigapil in CMD, if they confirm the results of the top line data already available, are unrelated to the potential outcome of any phase II efficacy trial of omigapil in CMD that we might decide to start in the future.

(3) The conduct of clinical trials may be prevented, delayed, or even futile, and delays in the commencement, enrollment or completion of clinical trials for any of our product candidates could result in increased costs, or prevent us from commercializing our product candidates on a timely basis, or at all.

Before a clinical trial may begin, we or our partners must obtain approval from the competent regulatory authority and/or the competent ethics committee. We or our partners may not obtain authorization for further testing of our product candidates. Clinical trials of our product candidates may not be conducted as planned, and commencement, enrollment or completion may not occur on our planned schedule, if at all, for many reasons, which could result in increased costs and could negatively affect our or our partners' ability to complete the clinical trial. We have experienced delays in clinical trials and cost overruns in the past and may do so again in the future. If we or our partners are not able to successfully design, operate, complete and correctly evaluate the results of the clinical trials for our product candidates, we will not be able to seek marketing authorization or commercialize them.

(4) If we or our partners experience delays or difficulties in the enrollment of patients in clinical trials, the conduct and completion of clinical trials may be delayed or prevented. Also, the availability of idebenone from inexpensive sources may adversely affect patient enrollment or the results of our clinical trials.

Initiation and successful and timely completion of clinical trials requires us to enroll a sufficient number of eligible patients in these trials. Given our focus on orphan drugs, our clinical trials look to enroll patients with characteristics that are found in a small number of patients and are likely to compete with other clinical trials for product candidates targeting treatment of patients with the same characteristics. As the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials in these clinical trial sites. As idebenone can be purchased over the internet and via other inexpensive sources, patients may be reluctant to enroll in our clinical trials where they do not know whether they will receive idebenone or a placebo. Also, the parallel use of idebenone by patients in the placebo arm of a trial may adversely affect the results of our clinical trials.

Delays in patient enrollment may result in increased costs or may affect the timing or outcome of our clinical trials, which could prevent their completion. We are, for example, in the process of enrolling patients for a phase III clinical trial (SIDEROS) for Raxone® in certain DMD patients. Enrollment is still ongoing and has been slower than anticipated. Based on our current estimates, we expect top line data of the SIDEROS trial to become available in 2020. Should there be any further delays in patient enrollment or if we are unable to recruit enough patients, the SIDEROS trial (and, consequently, the availability of any data) could be significantly delayed or even prevented.

(5) We may not be successful in our efforts to build up our pipeline of product candidates or to spend our limited resources on the most promising product candidates.

We may not be able to develop our existing product candidates or identify and develop further product candidates that are safe and effective despite spending substantial technical, financial, and personnel resources thereon. Because we have limited resources, we may forgo or delay pursuit of opportunities with certain product candidates or indications that later prove to have a greater potential than the product candidates or indications on which we have chosen to focus. Even if we are successful in continuing to build our pipeline, the product candidates that we identify may not be suitable for clinical development, including as a result of being shown to have harmful side effects or other characteristics that indicate that they are unlikely to receive marketing authorization and achieve market acceptance.

(6) We rely and will in the future rely on third parties to conduct clinical trials for our product candidates, and if they do not properly and successfully perform their obligations, we may not be able to successfully complete the respective development of our product candidates.

We rely on Clinical Research Organizations ("**CROs**") and other third parties to assist in managing, monitoring and otherwise carrying out clinical trials for our product candidates. Together with the salaries paid to our employees in the product development department, the fees and expenses of these CROs make up most of our development expenses. We compete with many other companies for the resources of these third parties. These third parties generally may terminate their engagements with us at any time.

If the quality or accuracy of the data that these third parties obtain is compromised due to their failure to adhere to clinical trial protocols or to regulatory requirements, or if they otherwise fail to comply with clinical trial protocols or meet expected deadlines, the clinical trials of our product candidates may not meet regulatory requirements. In one case, we had to terminate our relationship with a CRO for cause in 2016 and had to engage another CRO to complete the clinical trial conducted by the former CRO. If clinical trials

do not meet regulatory requirements or if these third parties need to be replaced for any reason, the development of our product candidates may be delayed or suspended, may be more expensive than planned or may ultimately fail.

Although we rely extensively on third parties to conduct our product development work, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with its general investigational plan, protocol, legal and regulatory requirements and scientific standards. We may incur financial liabilities or suffer negative regulatory consequences as a result of any shortcoming in meeting such responsibilities irrespective of whether we have delegated such responsibility to a CRO or other third party.

(7) We may not be successful in maintaining existing or establishing and maintaining additional collaborations.

We conducted the phase I clinical trial (CALLISTO) of our product candidate omigapil in CMD in collaboration with the National Institute of Neurological Disease and Strokes (the "**NINDS**"), an institute within the National Institutes of Health (the "**NIH**") in the U.S. This existing collaboration is, and any future collaborations or partnerships may be, important to our business. Generally, such collaborations allow us to share the development costs with our collaboration partners, thereby significantly reducing our own costs, and to utilize the expertise and know-how of our development partners. If a collaboration partner collaborates with us after assessing the viability of a product candidate, we also consider this a validation of our own development effort.

We may not be able to maintain our current or any future collaborations or partnerships, including for reasons beyond our control. In the event of termination of a collaboration, we may be unable to progress the relevant product candidate on our own or may be unable to successfully find a new partner with which to do so on terms favorable to us or at all. Also, any termination of a collaboration by our partner could make it difficult for us to attract new strategic partners or adversely affect how we are perceived in scientific and financial communities.

We will face significant competition in seeking partners for future product development collaborations. In order for us to successfully partner our product candidates, potential partners must view the respective product candidate as attractive, also in light of the terms that we are seeking. Even if we successfully establish new collaborations, their terms may not be favorable to us.

If we fail to establish or maintain a collaboration related to a particular product candidate, we will bear all of the related development cost and risk and may be unable to develop that product candidate on our own for lack of resources or other reasons.

(8) If serious adverse events or undesirable or unacceptable side effects are identified during the development of any of our product candidates or after commercialization of any product or any future products, we may need to abandon the development of the product candidates or withdraw the product from the market.

If any of our product candidates cause undesirable or unacceptable side effects in clinical trials or have characteristics that are unexpected, we may decide or be required to interrupt, delay or abandon the relevant product candidate's development or may choose to limit its development to more narrow uses or patient subpopulations in which such side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Serious procedure- or treatment-related side effects may occur at any stage of product development and even after commercialization. Any such side effects may cause us to abandon or limit the development of the relevant product candidate or we may decide or be required to withdraw the relevant product from the market, which may result in a sudden and sharp drop of our net

sales and/or significant impairment charges. These risks are amplified by the fact that we rely on one lead compound, idebenone, for use in our only marketed product, Raxone® in LHON and our only late-stage product candidate, Raxone® in DMD.

3. Risks related to marketing approval of our product candidates and legal compliance matters

(1) Following clinical development, our product candidates will require marketing authorization. If we are not able to obtain marketing authorization for a particular product candidate in a timely manner, on terms acceptable to us or at all, we will not be able to commercialize it, and our ability to generate sales will be materially impaired.

Our product candidates require marketing authorizations from the FDA in the U.S., from the European Commission in the EU and from comparable regulatory authorities in other relevant jurisdictions (such as Swissmedic in Switzerland), prior to commercialization. In most jurisdictions, the process of obtaining marketing authorization for a product candidate is expensive and may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Failure to obtain marketing authorization for a product candidate will prevent us from commercializing the product candidate.

Our experience in filing and supporting the applications necessary to gain marketing authorization for a product candidate is limited and some of our marketing applications were not successful. So far, only two marketing authorizations for our product, Raxone® in LHON, have been granted: we received marketing authorization for our product from the European Commission, and our exclusive distributor received marketing authorization for it from the Israeli Ministry of Health. We also filed MAAs with the EMA and with Swissmedic for Raxone® in certain DMD patients, but failed to receive marketing authorization for the EU and, as a result, withdrew our MAA with Swissmedic. We have never filed an NDA with, or obtained marketing authorization from, the FDA in the U.S., which is a significant pharmaceutical market. We have started (but may fail) to build up our in-house capacity for purposes of obtaining marketing authorization for Raxone® in DMD in the U.S., and we continue to rely on external advisors to assist us with the marketing authorization process in the U.S.

Regulatory authorities have substantial discretion in the timing and substance of the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. For example, the CHMP, when it issued its negative opinion on our MAA for Raxone® in certain DMD patients in the EU, considered that the effect of Raxone® on patients' respiratory function observed in our phase III clinical trial of Raxone® in certain DMD patients with declining respiratory function who were not receiving steroids (DELOS) could be clinically relevant if it would be maintained over several years, rather than the 52 weeks observed in the DELOS trial. The CHMP also expressed concerns about the way the study was conducted and analyzed. Moreover, there is considerable uncertainty around whether the FDA would accept an NDA filing based on the limited data from our DELOS trial, and it is possible that the FDA may not consider the SIDEROS trial, or any additional studies for Raxone® in DMD performed and completed that it may request, sufficient to approve any NDA for Raxone® in DMD that we may submit. If our clinical data are found insufficient, we may be forced to abandon an MAA for the EU or an NDA for the U.S. with respect to Raxone® in certain DMD patients.

Regulatory authorities may also narrow the uses or patient subpopulations for which the product is approved or require extensive warnings on the label, thereby limiting the potential market for or interest in the product.

If we experience delays in obtaining or fail to obtain marketing authorizations for any of our product candidates in any key jurisdiction, especially in the U.S. and the EU, their commercial prospects may be harmed

or they may no longer be commercially viable. As a result, our ability to generate sales will be materially impaired.

(2) Fast track, breakthrough therapy and similar designations for some of our product candidates may not lead to a faster development or regulatory review or approval process, will not increase the likelihood of receiving marketing authorization and may be revoked.

We have received fast track designation and rare pediatric disease designation from the FDA for Raxone® in DMD and for omigapil in CMD. We may seek fast track or similar designations for POL6014 in CF and/or any future product candidates. Further, the UK's Medicines and Healthcare Products Regulatory Agency (the "**MHRA**") gave certain DMD patients access to Raxone® under the Early Access to Medicines Scheme ("**EAMS**") following its designation as Promising Innovative Medicine ("**PIM**") by the MHRA. We may seek, but may not necessarily receive designations comparable to breakthrough therapy designations or PIM in other jurisdictions and for other products or product candidates.

Regulatory authorities typically have broad discretion in granting fast track, break through therapy, PIM and similar designations and may rescind or revoke such designations. Even if such designation is granted, such designation is not predictive of future clinical trial results, does not necessarily (and in the case of certain designations will not) result in a faster development process, review or marketing approval compared to conventional approval procedures and does not increase the likelihood that a product candidate will receive marketing authorization. Many drugs that have received such designations have failed to obtain marketing authorization. If we fail to obtain any such designation for a product candidate that we think meets the criteria or any existing designations is revoked, further development of that product candidate and, ultimately, its commercialization could be materially adversely affected.

(3) Our marketed product Raxone® in LHON is, and any product candidate for which we may obtain marketing authorization will be, subject to extensive post-marketing regulatory requirements and could be subject to post-marketing restrictions, post-marketing studies or withdrawal from the market, and we may be subject to penalties if we or the third parties with which we collaborate fail to comply with regulatory requirements or experience unanticipated problems with that product.

Our commercialization activities with respect to Raxone® in LHON (our marketed product) are, and any product candidates for which we may receive marketing authorization will be, subject to comprehensive regulation by regulatory authorities in each jurisdiction in which it is authorized. This regulation includes requirements regarding the testing, manufacture, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution of the relevant product. For example, for any marketed product we will need to submit safety and other post-marketing information and reports, ensure that our contract manufacturers observe current Good Manufacturing Practice ("**cGMP**") requirements and comply with requirements regarding safety monitoring and pharmacovigilance.

Regulatory authorities may also impose requirements for expensive post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. For example, under the European Commission's marketing authorization that was granted for Raxone® in LHON "under exceptional circumstances" because the European Commission found that comprehensive efficacy and safety data cannot be obtained, we are required to conduct several post-authorization measures, which include an additional phase IV clinical trial on the long-term effects and safety of Raxone® in LHON and a second comparative natural history study that we are currently conducting, as well as maintenance of a registry of LHON patients treated with Raxone®.

Also, if we refile an MAA for Raxone® in certain DMD patients with the EMA based on additional data in the future, even if the CHMP recommends that the European Commission grant marketing authorization,

such marketing authorization would very likely be subject to the condition that we conduct a post-authorization safety study ("**PASS**") and an externally controlled long-term open label study as post-authorization measures. Any such requirements for Raxone® in DMD or for any other products for which we may receive marketing authorization in the future may adversely affect our profit and cash flow generated from the relevant products, and such additional clinical trials involve the risks associated with any clinical trials. For example, if our phase IV clinical trial of Raxone® in LHON does not establish the product's long-term efficacy, this may impact its commercial success. Also, later discovery of previously unknown adverse effects or other problems with our products, manufacturers or manufacturing processes, or non-compliance with regulatory requirements may have serious consequences for us, including legal or regulatory actions such as warning letters, suspension of manufacturing, seizure of product, injunctions, withdrawal of the relevant product from the market and sanctions.

(4) Our relationships with customers and third-party payers and our general business operations are and will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm or diminished earnings, among other penalties.

Healthcare providers and third-party payers play a primary role in the recommendation and prescription of Raxone® in LHON and any product candidates for which we may obtain marketing authorizations. The arrangements with healthcare professionals, third-party payers and customers that we or our distributors have entered or will enter into may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we or our distributors market, sell and distribute our products (for which we receive marketing authorization). Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. If authorities conclude that our or our distributors' business practices do not comply with applicable laws and regulations, we or our employees or distributors may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government-funded healthcare programs such as Medicare and Medicaid, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, or the curtailment or restructuring of our operations.

(5) If we or our third-party contractors or employees fail to comply with environmental, health and safety laws, we could become subject to civil or criminal penalties, other remedial measures or incur costs that could harm our business.

We are subject to a variety of environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of biological materials and hazardous materials and wastes. The operations of our third-party manufacturers and suppliers involve the use of hazardous and flammable materials, including chemicals and biological materials, and also produce hazardous waste products. We cannot eliminate the risk of contamination or injury from these materials or wastes. In the event of such contamination or injury, we could be held liable for any resulting damages, and any liability could exceed our insurance coverage and our own resources. Non-compliance by us or our third-party contractors or employees with environmental, health and safety laws and regulations may result in substantial fines, civil or criminal penalties or other sanctions. In addition, we may incur substantial costs in order to comply with such laws and regulations.

4. Risks related to the commercialization of our product candidates and marketing and sale of our products

(1) Our marketed product, Raxone® in LHON, and any of our product candidates (to the extent we receive marketing authorization for them) may fail to achieve the degree of market acceptance by physicians, patients, third-party payers and others in the medical community necessary for commercial success despite having received marketing authorization.

Raxone® in LHON (our marketed product), and any product candidates, if any, for which we receive marketing authorization in the future, may fail to gain sufficient market acceptance by physicians, patients, third-party payers and others in the medical community despite having received marketing authorization. For example, other novel products may be preferred to our product. If any such products do not achieve an adequate level of acceptance, we may not generate significant product sales and we may not become profitable.

(2) Off-label and unlicensed uses of currently available forms of idebenone may adversely affect our sales of Raxone®.

Physicians may prescribe available products containing idebenone (the active ingredient in Raxone®) for uses for which they are not approved, such as the treatment of LHON or DMD, if they view such products as a less expensive treatment or a better alternative to Raxone®. A considerable number of physicians in Europe, and to a lesser degree in the U.S. and other countries, have been prescribing or recommending products containing idebenone to their patients on an off-label basis. The off-label product is either acquired from internet sources or in countries where it is approved and marketed for a different indication. By way of example, and without any claim to completeness:

- Takeda's Mnesis®, 45mg tablets containing idebenone, is registered in Italy for the treatment of "cognitive-behavioral deficits resulting from cerebral pathologies whether from vascular or degenerative origin" and is used off-label and prescribed as an unlicensed medicine for the treatment of other (non-approved) indications in Italy and in certain other countries.
- Sweden's Medical Products Agency ("**MPA**") has granted several licenses to individual patients for the prescription and reimbursement of Mnesis® for the treatment of LHON. We have initiated a number of court proceedings to challenge these MPA decisions. The Swedish Supreme Administrative Court has not granted leave to appeal first instance decisions that we do not have standing to challenge the respective licenses. Consequently, several of these court proceedings have been dismissed. However, there are also court proceedings pending based on new case law supporting that we should have standing to challenge the respective licenses. While we believe, based on advice of our counsel, that refusing us standing to challenge the respective licenses is an erroneous application of law, there can be no assurance that the administrative courts will agree with our view.
- Pharmacies have been compounding idebenone.

Any off-label or unlicensed use of idebenone, especially from inexpensive sources, and any reimbursement for such use granted by third-party payers may reduce our potential sales of Raxone®.

(3) We have only started to develop our marketing and sales organization, have limited experience in marketing products and do not expect to have significant marketing synergies between our current marketed product and, if and when approved, our current product candidates. If we are unable to establish and expand our marketing and sales capabilities or enter into distribution agreements with third parties, we may not be able to generate product sales.

We have only started to develop our own marketing, sales and distribution capabilities and have yet to commercialize Raxone® in LHON outside the EU. We have limited experience in marketing products in Europe and have no experience in marketing products in the U.S. and elsewhere. We are marketing Raxone® in LHON in European countries through a small internal sales and marketing force that we have been building up since January 2015, through the third-party distributor Ewopharma in eleven countries in Eastern Europe and the Baltics and the third-party distributor Pharmathen in Greece and Cyprus, each on an exclusive basis. In the U.S., our team currently manages our patient advocacy interactions, prepares for market entry in the U.S. and is the source of our U.S. regulatory and medical affairs expertise, whereas commercialization will only be possible if we file an NDA with, and receive marketing authorization from, the FDA regarding Raxone® in DMD.

In connection with the further rollout of Raxone® in LHON in the EU, and as a result of the ramp up of our activities in the U.S., we will need to develop further in-house marketing, sales and distribution capabilities. All of these activities are associated with an increase in the headcount of our marketing and sales personnel and of the related overhead and higher overall fixed costs, and will also require significant management resources and time. At the same time, we may engage additional third-party distributors to perform marketing, sale and/or distribution services. Any income that we receive or may receive from our current or future third-party distributors will depend upon the efforts of such distributors, over which we may have little or no control. We may not be able to develop and expand in-house marketing, sales and distribution capabilities or establish or maintain relationships with third-party collaborators to successfully commercialize Raxone® in key markets and for particular indications, which would adversely impact our ability to generate product sales.

Raxone® in LHON and each of our product candidates (if approved) will have different prescriber bases: primarily ophthalmologists in the case of Raxone® in LHON, primarily neurologists in the case of Raxone® and vamorolone in DMD and omigapil on CMD, and primarily pulmonologists in the case of POL6014 in CF. As a result, we expect to have somewhat limited marketing synergies between our products and may have to build separate sales channels for each of our products, which is expensive and may result in our products suffering from low profit margins or a lack of profitability.

(4) We face substantial competition, which may result in others discovering, developing or commercializing competing products before or more successfully than we do, as well as reducing the price at which we are able to sell our products.

The development and commercialization of new products is highly competitive. For instance, we believe that companies that are currently developing new products for the treatment of LHON (which may compete with our own product, Raxone®) may be granted marketing authorization during the next several years. Also, to our knowledge, two treatments for DMD developed by third parties that are not based on steroids have been approved to date, and there are a number of phase II clinical trials of drugs targeting muscle weakness in DMD. The fact that our lead compound, idebenone (the active ingredient in Raxone®), does not enjoy composition of matter patent protection lowers entry barriers for competitors.

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 or are better marketed than Raxone® in LHON or any product candidates for which we

receive marketing authorization. Our competitors may obtain marketing authorizations for their products more rapidly than we do, which could result in them establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected by third-party payers seeking to encourage the use of products that are less expensive than ours.

(5) Should we or our distributors be found to have improperly promoted off-label uses, we may become subject to significant liability.

Given that our marketed product, Raxone® in LHON, is also a product candidate for DMD, physicians may prescribe Raxone® to their patients in a manner that is inconsistent with our existing marketing authorizations in the EU and (via our exclusive distributor) in Israel or any future marketing authorizations. If we cannot successfully manage the marketing of our products by restricting off-label promotion or if we or our current or future distributors promote our products beyond their approved indications, we could become subject to enforcement action for off-label promotion and significant liability.

(6) The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain coverage and adequate reimbursement for our marketed product or any product for which we receive marketing authorization in the future and price controls could limit our ability to market those products and decrease our ability to generate sales.

The availability and extent of coverage and reimbursement by governmental and private third-party payers is essential for most patients to be able to afford expensive treatments. Sales of Raxone® in LHON (our marketed product) and any products for which we receive marketing authorization in the future will depend substantially on the extent to which the costs will be paid by third-party payers. Also, we rely on the efforts of our exclusive third-party distributor Ewopharma to obtain pricing and reimbursement approvals in eleven countries in Eastern Europe and the Baltics, as well as other third-party distributors, and may enter into similar arrangements with other third parties for other territories. We may have little or no control over the efforts of such third parties.

Seeking third party reimbursement is a time-consuming and expensive process, which typically requires us to provide scientific and clinical support and pharmaco-economic arguments for the use of the relevant product to each third-party payer separately. We may need to conduct expensive pharmaco-economic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, and third-party payers may nonetheless refuse reimbursement. Also, one third-party payer's decision to provide coverage for a product does not assure that other payers will also provide coverage, and pricing negotiations may continue after reimbursement has been obtained. The sales uptake of Raxone® in LHON in 2016 and 2017 was slower than originally expected due to the complex pricing and reimbursement processes in several EU markets and may continue to be slower than originally expected. Full reimbursement of Raxone® in LHON has been achieved for Germany, the Netherlands, Italy, Sweden, Scotland and six other jurisdictions. In several other jurisdictions, including France and England and Wales, Raxone® in LHON is currently covered by special reimbursement schemes. Third-party payers in several major EU countries have rejected our requests for pricing and reimbursement and we have been involved in legal proceedings in relation to such decisions. Even where reimbursement was approved or may be approved in the future, we had or may have to grant a significant discount on the list price and may have to reduce the price further in the future. Irrespective of the level of initial pricing, we expect the prices of our current and any future products to erode substantially during any market exclusivity period. We expect such price erosion to be accelerated after we have lost any such market exclusivity.

If reimbursement is not available or only to limited levels, we may not succeed in commercializing a product even if marketing authorization has been obtained. Even if coverage is provided, the approved reimbursement amount may not allow us to realize a sufficient return on our investment.

(7) Recently enacted and future healthcare reform legislation involves a high degree of uncertainty and may adversely affect our business.

We operate in a highly regulated industry. New laws, regulations or judicial decisions, or new interpretations of existing laws, regulations or decisions, related to healthcare availability, the method of delivery or payment for healthcare products and services could adversely affect pricing, reimbursement, marketing or sales of our marketed product or any product candidates for which we may receive marketing authorization in the future. In the United States and other jurisdictions, there have been a number of legislative and regulatory changes, proposed changes and statements by the current President of the United States regarding the pharmaceutical industry and the healthcare system that could prevent or delay marketing authorization and pricing and reimbursement approvals of our product candidates or make them more expensive, or their terms less attractive, or restrict or regulate post-approval activities. In particular, we may face uncertainties as a result of U.S. federal legislative and administrative efforts to repeal, substantially modify or invalidate some or all of the provisions of the Patient Protection and Affordable Care Act as amended by the Health Care and Education Reconciliation Act (collectively, the "**PPACA**"). A repeal or replacement of the PPACA, if it occurs, may adversely affect our business and financial results. All of these enacted or future measures may prevent us from generating sales, attain profitability, commercialize or market our products.

(8) Pharmacies have been compounding idebenone. Future compounding may adversely affect our sales of Raxone®.

Compounding (also called pharmacy or magistral preparation) is a practice in which a licensed pharmacist prepares medicines in a pharmacy by combining, mixing, or altering pharmaceutical ingredients. Under certain conditions, the sale of compounded idebenone (the active ingredient of Raxone®) is legal. In the EU, such compounding exemption is based on Article 3 of the EU Directive 2001/83. We are aware of pharmacies in Germany and the Netherlands that advertised compounded idebenone on the internet for the treatment of LHON, DMD and other indications at considerably lower prices than we charge for Raxone® in LHON, sometimes making reference to the clinical trials of Raxone® that we have conducted.

Compounding of idebenone has also resulted in litigation: a pharmacist in Germany filled capsules with generic idebenone purchased from a third party and advertised their sale on his website. In August 2017, the Landgericht Hamburg prohibited the pharmacist's advertising and sale of idebenone capsules, holding among other things that the portioning of the active pharmaceutical ingredient and filling of capsules are not covered by the compounding privilege. The pharmacist has appealed this decision. In addition, we are aware of the case of an LHON patient in Austria whose third-party payer—a major third-party payer in Styria, Austria—decided to reimburse the costs of compounded idebenone, but not of Raxone®. The patient successfully challenged this decision in court and the third-party payer must reimburse the costs of Raxone®. Further, we are aware that a major third-party payer in Vienna denied a LHON patient the reimbursement of Raxone®, arguing that pharmacists preparations are more cost efficient; this patient has initiated legal proceedings against the third-party payer.

Irrespective of the outcome of these cases, compounding of idebenone still continues and, consequently, reduces our sales of Raxone® in LHON and, eventually, if we receive marketing authorization, in DMD.

(9) Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of our marketed product or any product candidates for which we receive marketing authorization in the future.

We face an inherent risk of product liability exposure related to our commercialization of Raxone® in LHON (our marketed product) and any product candidate for which we receive marketing authorization in

the future, as well as to the use of our product candidates in humans in clinical trials. If we cannot successfully defend ourselves against claims that our products or product candidates caused injuries, we may incur substantial liabilities.

We currently have product liability insurance for Raxone® in LHON and insurance for human clinical trials covering all clinical trials conducted by us. However, our current product liability coverage may not be adequate in scope to protect us in the event of a successful product liability claim. Further, we may not be able to maintain our current insurance or obtain product liability insurance for any products for which we may receive marketing authorization in the future on reasonable terms and at acceptable cost, and our insurance may in any event provide insufficient coverage against potential liabilities. As a result, we may have to bear substantial uninsured losses.

(10) Our future profitability may be adversely affected if our estimates regarding the size of the market for our products and product candidates are inaccurate.

We based our estimates regarding the size of the market for our products and product candidates on our experience and our evaluation of market conditions, using publicly available information. In formulating these estimates, we made certain assumptions, which have not been verified by third parties. If our assumptions are incorrect, there is a risk that our estimates could be wrong and our future profitability may be adversely affected.

5. Risks related to market exclusivity rights and intellectual property

(1) Our business model relies on orphan drug exclusivity for our marketed product, Raxone® in LHON, and most of our current or future clinical product candidates. Orphan drug designation can be difficult to obtain and maintain, and it provides only limited protection from competition.

It is our strategy to develop and commercialize product candidates in indications qualifying for orphan drug designation in order to obtain marketing exclusivity. The market exclusivity period of an orphan drug designation is generally shorter than a patent protection period. In the U.S., for instance, such period is seven years, and in the EU, it is 10 years (reduced to six years if the relevant drug no longer meets the criteria or is sufficiently profitable) after receipt of marketing authorization. Also, orphan drug exclusivity may be lost if the applicable regulatory authority determines that the request for designation was materially defective, if the manufacturer is unable to assure sufficient quantity of the drug to meet patient needs, or for other reasons.

To date, we have obtained orphan drug designations (a) for our marketed product, Raxone® in LHON, in the EU (maximum duration until fall 2025), the U.S. and South Korea; (b) for our product candidate Raxone® in DMD, in the EU and the U.S.; (c) for our product candidate omigapil in CMD, in the EU and the U.S.; and (d) for POL6014 in alpha-1 antitrypsin deficiency ("**AATD**"), primary ciliary dyskinesia ("**PCD**") and cystic fibrosis ("**CF**") in the EU. We plan to seek orphan drug designation for POL6014 in CF in the U.S. as well, but may fail to obtain it. Vamorolone has received orphan drug designation in the U.S. and in the EU. We have not filed for orphan drug designation in all national and regional jurisdictions where such protection may be available; instead, we have sought such protections only with respect to jurisdictions that we currently anticipate being key to our business.

Obtaining an orphan drug designation can be difficult, and we may not be successful in obtaining or maintaining orphan drug designations for our marketed product or any of our product candidates. The procedure for obtaining orphan drug designation is an independent procedure in each jurisdiction, and applications might be denied in some jurisdictions, but granted in others. Further, orphan drug designation may be obtained for the same product in the same indication by several parties, and only the first such party to obtain

marketing approval will receive marketing exclusivity for the relevant product in the relevant indication. Consequently, despite us having obtained an orphan drug designation for a product candidate in a particular indication, if a third party were to obtain orphan drug designation and marketing authorization and the correspondence market exclusivity for the same product in the same indication, we would be excluded from marketing such product in such indication during the applicable exclusivity period.

If we lose orphan drug designation or fail to maintain that designation for the duration of the applicable exclusivity period in relation to our marketed product or, after receipt of marketing authorization (if any), any of our product candidates, we may be unable to generate sufficient sales from such product or product candidate to become profitable.

(2) Our marketed product, Raxone® in LHON, is not patent protected and we may only be able to seek limited patent protection, if at all, for most of our product candidates. Even granted patents may not be enforceable, and we may be subject to ownership disputes over patents or other intellectual property.

As the composition of matter patent for our lead compound, idebenone (the active ingredient in Raxone®) has expired, we can only seek method of use patent protection, as we have done for the use of idebenone to treat DMD. Typically, the protection derived from method of use patents is not as strong as the protection derived from composition of matter patents. Method of use patents do not prevent a third party from using, applying or manufacturing the same compound for other indications and may not prevent a third party from finding a way to circumvent the patent. For these reasons, a third party may be able to use idebenone in different or comparable formulas, applications or indications. Further, method of use patents are, in general, more susceptible to invalidity attacks by third parties than composition of matter patents.

Raxone® in LHON (our marketed product) is not patent protected. Our method of use patents for the use of Raxone® in DMD are due to expire in March 2026 in the EU, Japan, and the U.S. Most composition of matter patents for omigapil, including those in the U.S. and the EU, with regard to which we have an exclusive license from Novartis Pharma AG ("**Novartis**"), have expired. Our method of use patents for the use of omigapil in CMD in the U.S., the EU and other jurisdictions are due to expire in 2026 or 2027, as applicable. The composition of matter patents with respect to POL6014 held by Polyphor and certain other parties and exclusively licensed or sublicensed, as applicable, to us, are due to expire in 2025, subject to potential extended market protection. Vamorolone is protected by method of use patents held by ReveraGen for a number of indications, including muscular dystrophy. ReveraGen's method of use patents for the treatment of muscular dystrophy are due to expire in 2029. Further, we may not be able to rely on patent protection for any of our future product candidates.

The patent applications that we own or in-license may fail to result in issued patents with claims that cover our product candidates in certain countries. There is no assurance that all potentially relevant prior art relating to such patents and patent applications has been identified. We may be unaware of prior art that could be used to invalidate an issued patent or prevent pending patent applications from issuing as patents. Even if patents do successfully issue and even if such patents cover our product candidates, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Without extensive patent protection, we will only be able to rely upon the time-limited market exclusivity, if any, resulting from any orphan drug designation, which may be revoked, will only apply for a limited time period and will be subject to other conditions and limitations. If we are unable to obtain, or if we or our licensors or sublicensors lose, patent protection with respect to any of our products or product candidates, we may be unable to prevent competitors from entering the market with a product that is similar to or the same as our product or product candidate. Further, we may be subject to ownership disputes over patents or other intellectual property with licensors, sublicensors, former employees, collaborators or other third parties.

(3) We have in-licensed our early stage pipeline and other intellectual property, and have acquired an option to in-license vamorolone, from third parties. We could lose our rights to use the licensed intellectual property in the event of termination of or dispute relating to the relevant license or if such intellectual property is unenforceable for any reason. In addition, enforcement of in-licensed intellectual property and defending against third-party claims in relation thereto are more complex than in the case of our own owned intellectual property.

We have acquired an exclusive option to obtain from Idorsia an exclusive sub-license to commercialize ReveraGen's vamorolone, subject to an upfront payment of USD 20.0 million to Idorsia and the issuing of 1,000,000 Shares to Idorsia. We will be able to exercise this option against payment of USD 30.0 million at the latest when the data from the Phase IIb study in DMD patients are available. In addition, we have in-licensed omigapil from Novartis and POL6014 from Polyphor, in each case on an exclusive world-wide basis. The same risks that apply to the intellectual property rights we own generally apply with respect to protection of intellectual property that we license. If we or our licensors fail to prosecute, maintain and enforce such intellectual property or if such intellectual property is unenforceable or if a licensor would enter bankruptcy or similar distressed status, we could lose our rights to use such intellectual property or our exclusivity with respect to those rights. The same may be the case if the agreements by which we have in-licensed or under which we have the option to in-license intellectual property are terminated or if a dispute arises between us and our licensing partners in relation to our rights or obligations under the license or option agreements, including any such conflict, dispute or disagreement arising from our failure to satisfy payment obligations under any such agreements. In addition, the enforcement of in-licensed intellectual property in case of violations or misappropriation by third parties and defending against third-party claims in relation to in-licensed intellectual property are more complex than in the case of owned intellectual property. Such proceedings may require coordination with the licensor, and licensors typically have rights to intervene or veto rights. As a result of these factors, our ability to develop and commercialize the affected product candidates may be adversely affected and we may not be able to prevent competitors from making, using, and selling competing products.

(4) Third-party claims of intellectual property infringement or misappropriation may prevent or delay our product development and commercialization efforts.

There is a substantial amount of litigation involving patent and other intellectual property rights in the pharmaceutical and biotechnology industries, including patent infringement lawsuits, interferences, oppositions and *inter partes* reexamination proceedings before the government patent offices. Numerous patents and pending patent applications owned by third parties exist in the fields in which we are active. Third parties may assert that we infringe their intellectual property, and patent applications covering our product candidates could have been filed by others without our knowledge. We may also face a claim of misappropriation if a third party believes that we inappropriately obtained and used trade secrets of such third party. Parties making claims against us may obtain injunctive or other equitable relief that could effectively prevent us from further developing or commercializing our product candidates or marketing our product or any future products. We have not conducted a freedom-to-operate search or analysis for our own or in-licensed products (including vamorolone). Thus, we may not be aware of third parties' intellectual property that our products, or our sale or commercialization thereof, may infringe or that, if issued, would block us from selling or otherwise commercializing our products. If any third-party patents were held by a court of competent jurisdiction to cover aspects of our materials, formulations, methods of manufacture or methods of treatment, the holder of any such patents would be able to block our ability to develop and commercialize the applicable product candidate until such patent expired or unless we or our partners obtain a license. These licenses may not be available on acceptable terms, if at all. Even if we or our partners were able to obtain a license, the rights may be non-exclusive, which could result in our competitors gaining access to the same intellectual property. Ultimately, we could be prevented from commercializing a product candidate, or be forced to cease some aspect of our business operations, if as a result of actual or threatened

patent infringement claims, we or our partners are unable to enter into licenses on acceptable terms. Defending against claims of patent infringement or misappropriation of trade secrets could be costly and time-consuming, regardless of the outcome, and result in significant demands on the time and attention of the management teams. In the event of a successful claim of infringement, we may be required to pay substantial damages, royalties or other financial remedies and incur other significant costs, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible, or require substantial time and monetary expenditure, or incur other significant costs and lose the patent protection to which we thought we were entitled.

During the course of any patent or other intellectual property litigation, there could be public announcements of the results of hearings, rulings on motions, and other interim proceedings in the litigation. If potential and current partners or collaborators or securities analysts or investors regard these announcements as negative, the perceived value of our technology, product candidates and products, development programs or intellectual property could be diminished.

Furthermore, the U.S. government has reserved certain rights to vamorolone. As a consequence, ReveraGen is required to comply with certain formalities, including in particular the filing of certain information with governmental databases. Whether or not ReveraGen complies with this requirement is beyond our control. Should ReveraGen be found to be, or have at any point been, in breach of such filing or other obligations in connection with vamorolone, this could result in the retransfer of intellectual property rights in connection with vamorolone to the U.S. Army Medical Research and Materiel Command (USAMRMC) or any successor or other governmental entity or authority and/or in any of ReveraGen, Idorsia and/or ourselves being involved in a litigation relating to intellectual property rights in connection with vamorolone, each of which could have a materially adverse effect on our business, results of operations, financial position and cash flows and potentially damage our reputation.

(5) We enjoy only limited geographical protection with respect to patents and may face difficulties in certain jurisdictions, which may diminish the value of intellectual property rights in those jurisdictions.

We and our licensors have not filed for patent protection in all national and regional jurisdictions where such protection may be available; instead, we have sought such protection only with respect to jurisdictions that we currently anticipate being key to our business, in particular the U.S. and the EU. In addition, we may decide to abandon national and regional patent applications before grant. Finally, the grant proceeding of each patent in each jurisdiction is an independent proceeding, and applications might in some jurisdictions be refused, while granted in others, which may ultimately limit our ability to rely on jurisdictional exclusivity, if any, for our marketed product or our product candidates in certain jurisdictions. Depending on the jurisdiction, the scope of patent protection may vary for the same product candidate or technology.

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws in the U.S. and Europe, and many companies have encountered significant difficulties in protecting and defending such rights in such jurisdictions. If we or our licensors encounter difficulties in protecting, or are otherwise precluded from effectively protecting, the intellectual property rights important for our business in such jurisdictions, the value of these rights may be diminished, and we may face additional competition from others in those jurisdictions.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we 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 and results of operation may be adversely affected.

(6) If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

We rely on trade secrets and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our technology and development processes that involve proprietary know-how, information or technology that is not covered by patents. In addition, we rely on our employees, advisors, third party contractors such as CROs, consultants and collaboration partners to develop and manufacture our product and product candidates, which is why we must, at times, share our intellectual property and trade secrets with them.

Trade secrets can be difficult to protect. We seek to protect our proprietary and in-licensed technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, and outside scientific advisors, contractors and collaborators, but our employees, consultants, outside scientific advisors, contractors and collaborators may intentionally or inadvertently disclose our trade secret information to competitors. In addition, our competitors may gain access to our trade secrets through legal or illegal means or independently develop substantially equivalent information and techniques. We may not be able to protect trade secrets effectively and we may not have adequate remedies against misappropriation of trade secrets. Enforcing a claim that a third party illegally obtained and is using any of our trade secrets is expensive and time consuming and the outcome is unpredictable. In addition, courts outside the U.S. sometimes are less willing than U.S. courts to protect trade secrets. Misappropriation, unauthorized disclosure or a competitor's discovery of our trade secrets could materially impair our competitive position or our business.

Many of our employees were previously employed at universities or other pharmaceutical companies, including our competitors or potential competitors. We may be subject to claims that we or our employees have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of our employees' former employers or other third parties. We may also be subject to ownership disputes in respect of intellectual property created by these employees during the course of their employment with us. Any of such claims could result in our competitive position being impaired and our business and results of operation may be adversely affected.

(7) We may become involved in lawsuits to protect or enforce our patents and other exclusivity rights, which could be expensive, time-consuming, and unsuccessful.

Competitors may infringe our intellectual property, the intellectual property of our licensors, or the market exclusivity resulting from orphan drug designations that we have achieved. To counter or defend against such claims can be expensive and time-consuming. In an infringement proceeding, a court may decide that a patent owned or in-licensed by us is invalid or unenforceable and/or may refuse to stop the other party from using the technology at issue. An adverse result in any litigation over exclusivity rights could put one or more of our or our licensors' patents at risk of being invalidated or interpreted narrowly or an orphan drug designation of being revoked. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation in many jurisdictions, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in the patents or other intellectual property we own or license-in. We may be subject to ownership disputes in the future arising from, for example, conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these

and other claims challenging inventorship or ownership. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and employees.

6. Risks related to manufacturing, employment matters, operations, managing growth, corporate structure and financial reporting

(1) We have no manufacturing capabilities or capacity of our own and rely on third parties for production of Raxone® and our other compounds, omigapil and POL6014.

We have no manufacturing capabilities or capacity of our own and have outsourced the entire manufacture, formulation, packaging, storage and distribution of Raxone® and our other compounds, omigapil and POL6014, to third parties. We currently have no plans to build up or acquire manufacturing capacity and the related know-how of our own in relation to omigapil and POL6014.

For the production of Raxone®, we rely on a drug substance supplier, with whom we have agreed on a seven-year exclusivity period (subject to exceptions) starting with the first launch of Raxone® in Europe and the U.S., respectively. In Europe, such exclusivity period will lapse in October 2022. We currently have one finished drug product supplier of Raxone®. If any of our manufacturing agreements is terminated or not renewed by the third-party provider, we may not be able to timely negotiate a new agreement with that or another third-party provider on acceptable terms or at all. Furthermore, switching a supplier of the drug substance or the finished drug product is an expensive and time-consuming process.

We rely on our licensor, Novartis, to provide omigapil. We primarily rely on Polyphor to supply the active pharmaceutical ingredient of the POL6014 compound. To the extent we may not be able to use Polyphor's inventory of the active pharmaceutical ingredient of the POL6014 compound, we rely on a third-party manufacturer of the POL6014 compound. We also rely on PARI Pharma GmbH, Gräfelfing, Germany, as the manufacturer of the nebulizer called eFlow® with which POL6014 is administered.

The facilities used by our suppliers to manufacture Raxone® and the finished products containing omigapil or POL6014 are subject to approval and inspections by regulatory authorities. We do not have full control over our suppliers' quality control or compliance with laws, regulations or cGMP standards, and any non-compliance could result in sanctions being imposed also on us, including fines, injunctions, civil penalties, delays, suspension, withdrawal or non-grant of market of approvals, seizures or recalls of products, operating restrictions and criminal prosecutions.

(2) The compounds we use are complex and difficult to manufacture. Only a handful of manufacturers are able to manufacture these compounds, and our manufacturers may experience production problems.

The manufacturing of our compounds necessitates compliance with regulatory requirements, such as cGMP, and is complex, time-consuming and expensive. In particular, only a handful of manufacturers are able to manufacture idebenone in compliance with all regulatory requirements. Manufacturing idebenone involves heavy metal catalysts, the incomplete removal of which in the manufacturing process would result in toxic amounts of these impurities remaining in the drug substance, and non-cGMP synthesis of idebenone may result in other toxic or cancerogenic by-products. Problems with the manufacturing process, even minor deviations from the normal process, could result in contamination, product defects or manufacturing failures that could result in harm to patients, lot failures, product recalls, product liability claims, or insufficient inventory. Regulatory authorities may require us to submit samples of any lot or may require that

we do not distribute a lot until the agency authorizes its release. Our contract manufacturers may be unable to achieve adequate quantities and quality of clinical-grade materials, and their supply chain could be interrupted from time to time. Any such problems could materially harm our business, financial condition, results of operations, and prospects.

(3) If we lose the services of any member of our top management or other key members of our management, scientific or commercial staff, or if we fail to attract and retain key scientific or other personnel, we may be unable to successfully develop and commercialize our product candidates or market our current marketed product or any future products for which we obtain marketing authorization.

We are highly dependent on the performance and expertise of members of our top management, especially our CEO, whose responsibilities include those of a Chief Scientific Officer, and other key members of our management, scientific and commercial staff. We are a small company with many key functions being carried out by one person only. The loss of the services of any of our key personnel for any reason or our inability to attract new highly qualified and experienced employees could harm our business. Furthermore, we do not currently maintain "key person" insurance for any of our executives or other employees.

A limited number of people have experience and know-how in neuro-ophthalmologic, neuromuscular and pulmonary diseases and the product and product candidates developed by us. To foster retention, we have established employee participation plans, but there is intense competition for skilled personnel. If our product candidates are granted marketing authorizations or if we expand our development activities, we would need to hire additional personnel, which may be difficult to recruit and retain on acceptable terms given such competition.

(4) We will need to grow the size and capabilities of our organization, and we may experience difficulties in managing this growth.

As of September 30, 2018, we had 119 employees (113.6 full-time equivalent) and we expect our headcount to increase in the near future in connection with the further rollout of Raxone® in LHON in the EU, as a result of the ramp up of our activities in the U.S., and as a consequence of our planned clinical development of POL6014. Our future financial performance will depend, in part, on our ability to effectively manage any future growth. We will need to expand and effectively manage our organization, personnel, operations and facilities in order to successfully develop and commercialize our marketed product and our product candidates. We will only be able to organize operations efficiently and avoid a misallocation of resources if we continue to improve our operational, financial and management controls, reporting systems and procedures. Our management may have to divert a disproportionate amount of its attention away from day-to-day activities in order to manage these growth activities. If we are unable to effectively expand our organization, we may not achieve our development and commercialization goals and our operational efficiency may be materially adversely affected.

(5) Our and our partners' computer systems may fail or suffer security breaches, which could result in a material disruption of our product development programs and our business operations.

Despite the implementation of security measures, our computer systems and those of our current and any future suppliers, CROs and other contractors, consultants and collaborators are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our product development programs and our business operations, whether due to a loss of our trade secrets or other disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs due to efforts to recover or reproduce the data. To the extent that any disruption or security breach

were to result in data loss or inappropriate disclosure of confidential or proprietary information or personal data of patients or other persons, we may be exposed to liability and suffer reputational damage.

7. Risks related to general economic and financial market conditions

(1) Changes in the macro-economic environment and political developments in Europe, the United States and elsewhere may have a material adverse effect on the Group and may reduce the value of our Shares.

Over the past years, there has been a series of political and economic events such as the past global economic financial crisis, sovereign debt and financial crises in several EU countries, the decision of the United Kingdom to leave the EU (commonly known as "Brexit"), the conflict in Syria, the 2016 U.S. presidential election and increased tensions in the Middle East. These events have impacted the global economy at large, the economies and financial situation of governments in many of our current and potential future markets, as well as exchange rates (in particular the euro/Swiss franc rate) and have been associated with, among other things, instability of financial institutions, high market volatility, liquidity problems, limited availability of financing and legal uncertainty. Recession or rising inflation and other effects may also be a consequence of these events. This uncertain macro-economic environment may have a material adverse effect on our business, results of operations, financial condition, prospects, or the market price of our securities, including our Shares.

(2) We are exposed to currency fluctuation risks and other financial risks.

While we incur costs mainly in Swiss francs, a significant proportion of our costs are required to be paid in euros. To the limited extent we generate sales, we receive payments primarily in euros. If and as our business grows, we expect that a significant part of our sales and a significant part of our expenses will be denominated in euros. Our reporting currency is the Swiss franc and, as a result, financial line items are converted into Swiss francs at applicable foreign exchange rates. Further, we are subject to interest rate risks. Unfavorable developments in the value of the Swiss franc as compared to the euro, in interest rates and in the capital markets could have a material adverse effect our financial condition and results.

B. Risks related to the Shares

(1) Shareholders may suffer dilution as a result of further issuance of equity, conversions of our Bonds or further issuances of other securities convertible into equity.

We may need or elect to raise additional equity or equity-linked financing in the future in order to continue our operations as planned. In addition, holders of our Bonds have the right to convert the Bonds before their maturity in 2022 into an aggregate of up to 925,926 Shares at a conversion price of CHF 64.80 per Share. Also, the Company has issued, and may issue in the future, other rights to acquire Shares. As of September 30, 2018, such rights to acquire 268,799 Shares (excluding conversion rights under the Bonds) were outstanding.

Additional dilution may occur to the then-existing shareholders if and to the extent that the Bonds will be converted and such rights to acquire Shares will ultimately be exercised and settled in Shares. Moreover, to the extent that the Company issues additional shares or equity-linked instruments (*e.g.*, for financing purposes or for employee participations), investors' ownership interest will be further diluted, and the terms of such issued shares may include liquidation or other preferences that adversely affect investors' rights as a shareholder.

(2) The Share price has been and is expected to be volatile.

The market price of the Shares has historically been subject to substantial fluctuations. We expect the market price of the Shares to continue to be highly volatile. Such volatility may depend upon many factors within and beyond our control, our or our competitors' financial and business performance, general market conditions and the volatility in financial and other markets (*i.e.*, the degree to which prices fluctuate over a particular period in a particular market, regardless of market levels) in general. In some cases, the markets have produced downward pressure on share prices for certain issuers seemingly without regard to those issuers' underlying financial strength.

(3) The trading market for the Shares is not liquid and shareholders may not trade or sell their Shares easily or at all.

The volume of the trading market for the Shares on the SIX Swiss Exchange has been low and is expected to be low in the future. Therefore, the trading market may not provide enough liquidity to allow shareholders to trade or sell their Shares easily or at all. The Company is not obliged to provide a bid or offer price for the Shares. Further, the Company's market making arrangement with Kepler Cheuvreux SA may be terminated at any time, and even while this arrangement is in place, there is no assurance that shareholders will be able to trade or sell their Shares easily or at all.

(4) Future sales of a substantial number of Shares or derivative instruments by us or our investors could adversely affect the market price of the Shares.

Sales, or the possibility or perceived possibility of sales, of a substantial number of Shares in the market could have a material adverse effect on the market price of the Shares. Any shareholders not subject to a lock-up agreement may sell some or all of their Shares in the open market at any time. Also, holders of Bonds have the right to convert the Bonds into Shares at any time before the maturity of the Bonds in 2022 and will be able to sell some or all of the Shares issued by the Company upon such conversion in the open market at any time. In addition, the Company may issue additional Shares out of its existing authorized share capital or may propose to its shareholders to approve additional capital increases, in each case excluding shareholders' preemptive rights. As a result of the respective issuances or sales of Shares, or if such issuances or sales are anticipated by investors, the market price of the Shares could fall substantially.

(5) The Company does not expect to pay dividends in the foreseeable future.

Since its inception, the Company has never paid any dividends and it does not anticipate paying dividends in the foreseeable future. Investors cannot rely on dividend income from the Shares, and any returns on an investment in the Shares will likely depend entirely upon any future appreciation in the price of the Shares and the ability of investors to sell Shares in the market.

(6) Shareholders outside Switzerland may not be able to exercise preemptive rights in future issuances of equity or other securities that are convertible into equity.

Under Swiss law, shareholders may have certain preemptive rights to subscribe on a pro rata basis for issuances of newly issued equity or other securities that are convertible into equity. Due to laws and regulations in their respective jurisdictions, non-Swiss shareholders may not be able to exercise such rights unless we take action to register or otherwise qualify the rights offering under the laws of that jurisdiction. There can be no assurance that we would take any such action, and we will have the full discretion to decide not to take such action in one or more jurisdictions, including the EU and the U.S. If shareholders in such jurisdictions are unable to exercise their subscription rights, their ownership interest in the Company would be diluted.

(7) Shareholders may face additional investment risk from currency exchange rate fluctuations in connection with their holding of Shares.

The Shares are and will be quoted in Swiss francs only, and future dividends, if any, will be denominated in Swiss francs. If the Swiss franc depreciates against a foreign currency that is the main currency of a shareholder, the value of the Shares or of any dividend, expressed in such foreign currency, will decrease accordingly. Prospective investors should be aware that exchange rates between currencies are highly volatile. Foreign exchange fluctuations between a shareholder's main currency and the Swiss franc may adversely affect shareholders who intend to convert the proceeds from the sale of the Shares or future dividends, if any, into their main currency and may potentially cause a partial or total loss of a shareholder's initial investment.

(8) If securities or industry analysts do not publish research at all or publish inaccurate or unfavorable research about the Group's business, the market price and/or the trading volume of the Shares could decline.

The trading market for the Shares depends in part on the research and reports that securities or industry analysts publish about the Group or its business. If no or few securities or industry analysts cover the Company, the market price for the Shares could be adversely affected. If one or more of the analysts who cover the Group downgrades a recommendation with regard to the Shares, publishes inaccurate or unfavorable research about the Group's business, ceases to cover the Group or fails to publish reports on it regularly, the market price and/or the trading volume of the Shares would likely decline.

(9) Our largest shareholders are able to exert influence over the Company, and their interests may not necessarily be the same as those of other shareholders.

The Company's largest shareholder is Idorsia who owns an aggregate of 13.3% of the voting rights in the Company. Idorsia and our other significant investors together own an aggregate of 32.26% of the voting rights in the Company. Any of our investors may start acting in concert or may acquire significant ownership interests in the Company in the future. Such shareholders or groups of shareholders may be able to exert influence over, and potentially block, certain matters that must be decided by the Company's general meeting of shareholders, in particular those matters that require the consent of two-thirds of voting rights represented. The influence of significant shareholders or groups of shareholders is accentuated by the low historic rates of participation at the Company's past three annual general meetings of shareholders, which were between 33.3% (2018) and 51.2% (2016). The interests of influential shareholders may not be the same as the interests of the Company's other shareholders, and respective corporate decisions may materially adversely affect the interests of the other investors in the Company.

(10) Our articles of association provide for an opting out of the mandatory tender offer rules. As a result, our shareholders would not have the possibility to sell their Shares in the event that a shareholder or group of shareholders acquires more than 33 1/3% of the voting rights in the Company. Also, the minimum price rules would not be applicable in any voluntary public tender offer for Shares in the Company.

Our articles of association exempt shareholders from the mandatory tender offer rules under the Federal Act on Financial Market Infrastructures and Market Conduct in Securities and Derivatives Trading of June 19, 2015 (the "**FMIA**") and its predecessor. As a result, any shareholder or group of shareholders exceeding the threshold of 33 1/3% of the voting rights (whether exercisable or not) of the Company would not be required to make a mandatory public tender offer for all Shares. Accordingly, our shareholders would not have the possibility to sell their Shares in the event that a shareholder or group of shareholders obtains control of the Company. Also, voluntary public tender offers may be made at less than the minimum price

under the mandatory tender offer rules (*i.e.*, the higher of the pre-offer 60-day volume weighted average price and the highest price paid by the offeror for equity securities within the last 12 months) even if the offeror would, as a result, hold more than 33 1/3% of the voting rights in the Company.