Filed pursuant to Rule 424(b)(3)
Registration No. 333-225676

PROSPECTUS SUPPLEMENT NO. 8

17,948,717 Common Shares

Auris Medical Holding AG

Common Shares

This Prospectus Supplement No. 8 (this "Prospectus Supplement") amends and supplements our Prospectus dated July 12, 2018 (the "Prospectus"), which forms a part of our Registration Statement (our "Registration Statement") on Form F-1 (Registration No. 333-225676). This Prospectus Supplement is being filed to amend and supplement the information included or incorporated by reference in the Prospectus with the information contained in this Prospectus Supplement. The Prospectus and this Prospectus Supplement relate to the resale of up to 17,948,717 of our common shares issuable upon exercise of certain outstanding warrants.

This Prospectus Supplement includes information from our Current Report on Form 6-K, which was filed with the Securities and Exchange Commission on January 29, 2019.

This Prospectus Supplement should be read in conjunction with the Prospectus that was previously delivered, except to the extent that the information in this Prospectus Supplement updates and supersedes the information contained in the Prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this Prospectus Supplement or the Prospectus. Any representation to the contrary is a criminal offense.

The date of this Prospectus Supplement is January 29, 2019.

Filing on Form F-4

On January 29, 2019, Auris Medical Holding AG (the "Company") filed a Registration Statement on Form F-4 (the "Registration Statement") containing a prospectus/proxy statement to be sent to shareholders in connection with an extraordinary general meeting of shareholders to be held to approve the redomestication of the Company from Switzerland to Bermuda. The following excerpts from the Registration Statement update the

information set forth under “Item 3. Key Information—D. Risk factors” and “Item 4. Information on the Company” in our Annual Report on Form 20-F for the year ended December 31, 2017.

RISK FACTORS

You should carefully consider the risks and uncertainties described below and the other information in this proxy statement/prospectus before making an investment decision with respect to our common shares. Our business, financial condition or results of operations could be materially and adversely affected if any of these risks occurs, and as a result, the market price of our common shares could decline and you could lose all or part of your investment. This proxy statement/prospectus also contains forward-looking statements that involve risks and uncertainties. See "Forward-Looking Statements." Our actual results could differ materially and adversely from those anticipated in these forward-looking statements as a result of certain factors.

Risks Related to Our Business and Industry

We are in the process of evaluating potential next steps in the development of our lead product candidate, Keyzilen® following the failure of the Phase 3 trial. In addition, we have initiated a strategic partnering process for our second lead product candidate Sonsuvi®. We cannot give any assurance that these candidates will continue to be developed, receive regulatory approval or be successfully commercialized or partnered.

We do not have any products that have gained regulatory approval. We have two lead clinical-stage product candidates, (i) Keyzilen® (AM-101), which is being developed for the treatment of acute inner ear tinnitus and (ii) Sonsuvi® (AM-111), which is being developed for the treatment of acute inner ear hearing loss. On March 13, 2018, we announced that preliminary top-line data from the TACTT3 Phase 3 clinical trial with Keyzilen® indicated that the study did not meet its primary efficacy endpoint of a statistically significant improvement in the Tinnitus Functional Index, or TFI, score from baseline to Day 84 in the active treated group compared to placebo either in the overall population or in the otitis media subpopulation. This followed our announcement in August 2016 that, TACTT2, the previously conducted Phase 3 sister trial with Keyzilen®, did not meet its two co-primary efficacy endpoints of statistically significant changes in tinnitus loudness and tinnitus burden compared to placebo. We are in the process of evaluating our options for the Keyzilen® development program, including whether we will continue to seek the development, regulatory approval and commercialization of either Keyzilen® in the future, or pursue an alternative course of action. If we continue development of Keyzilen®, we would need to conduct additional studies and trials in the future, in order to pursue regulatory approval and would need to raise additional capital to fund any such additional study, and we may be unable to secure such capital. If we are not able to raise additional capital, we may not be able to complete the development, testing and commercialization of Keyzilen®.

On November 28, 2017, we announced that the HEALOS Phase 3 clinical trial that investigated our other lead product candidate, Sonsuvi®, in the treatment of acute inner ear hearing loss did not meet the primary efficacy endpoint of a statistically significant improvement in hearing from baseline to Day 28 compared to placebo for either active treatment groups in the overall study population. However, in post-hoc analyses a clinically meaningful and nominally significant improvement in hearing was observed in the subpopulation of patients with acute profound hearing loss at baseline. Based on these results, we submitted the design of a new pivotal trial with AM-111 0.4 mg/mL in patients suffering from acute profound hearing loss to the EMA and subsequently also to the FDA for review. Through a Protocol Assistance procedure the EMA endorsed the proposed trial design, choice of efficacy and safety endpoints, as well as the statistical methodology. In a Type C meeting with written responses, the proposed choice of primary and secondary efficacy endpoints, the safety endpoints, as well as the planned sample size and statistical methodology were also endorsed by the FDA. Following this feedback, we have mandated a transaction advisory firm to identify potential partners for the Sonsuvi® development program and provide support for partnering discussions and negotiations. If successful, this may result in one or several sale, out-licensing or co-development transaction(s) on a global or regional scale. However, there is no guarantee that we will be successful in any pursuit of such strategic options or if we do continue our efforts to develop and commercialize Sonsuvi® in the future, or that any alternative course of action will lead to the success of the program.

We are a development-stage company and have a limited operating history and a history of operating losses. We anticipate that we will continue to incur losses for the foreseeable future.

We are a development-stage biopharmaceutical company with limited operating history. Since inception, we have incurred significant operating losses. We incurred net losses (defined as net loss attributable to owners of the Company) of CHF 7.8 million for the nine months ended September 30, 2018, and CHF 24.4 million, CHF 30.7 million and CHF 29.7 million for the years ended December 31, 2017, 2016 and 2015, respectively. As of September 30, 2018, we had an accumulated deficit of CHF 142.5 million.

Our losses have resulted principally from expenses incurred in research and development of our product candidates, pre-clinical research and general and administrative expenses that we have incurred while building our business infrastructure. We expect to continue to incur significant operating losses in the future as we continue our research and development efforts for our product candidates in clinical development. In our financial year ended December 31, 2017, we incurred CHF 19.2 million in research and development costs, and we expect that our total operating expense in 2018 will be in the range of CHF 10.0 to 13.0 million.

To date, we have financed our operations through the initial public offering and a follow-on offering of our common shares, private placements of equity securities and short- and long-term loans. On July 19, 2016, we entered into a Loan and Security Agreement with Hercules Technology Growth Capital, Inc., or Hercules. The agreement provides us with a senior secured term loan facility for up to $20 million. As of September 30, 2018, the amount outstanding under the Loan and Security Agreement was CHF 2.1 million.

We have no products approved for commercialization and have never generated any revenues from product sales. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. It may be several years, if ever, before we have a product candidate approved for commercialization and begin to generate revenues from product sales.

We have never generated any revenue from product sales and may never be profitable.

We have no products approved for commercialization and have never generated any revenue. Our ability to generate revenue and achieve profitability depends on our ability to successfully complete the development of, and obtain the marketing approvals necessary to commercialize, one or more of our product candidates. We do not anticipate generating revenue from product sales unless and until we obtain regulatory approval for, and commercialize, Keyzilen®, Sonsuvi®, AM-125 or AM-201. Our ability to generate future revenue from product sales depends heavily on our success in many areas, including but not limited to:

- completing research and clinical development of our product candidates;
- obtaining marketing approvals for our product candidates, including Keyzilen®, Sonsuvi®, AM-125 or AM-201, for which we will have to complete clinical trials;
- developing a sustainable and scalable manufacturing process for any approved product candidates and maintaining supply and manufacturing relationships with third parties that can conduct the process and provide adequate (in amount and quality) products to support clinical development and the market demand for our product candidates, if approved;
- launching and commercializing product candidates for which we obtain marketing approval, either directly or with a collaborator or distributor;
- obtaining market acceptance of our product candidates as viable treatment options;
- addressing any competing technological and market developments;
- identifying, assessing, acquiring and/or developing new product candidates;

- negotiating favorable terms in any collaboration, licensing, or other arrangements into which we may enter;
- maintaining, protecting, and expanding our portfolio of intellectual property rights, including patents, trade secrets, and know-how; and
- attracting, hiring, and retaining qualified personnel.

Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Because of the numerous risks and uncertainties with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Our expenses could increase beyond expectations if we are required by the FDA, the EMA, or other regulatory agencies, domestic or foreign, to change our manufacturing processes, or to perform clinical, nonclinical, or other types of trials in addition to those that we currently anticipate. In cases where we are successful in obtaining regulatory approvals to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to obtain coverage and reimbursement at any price, and whether we own the commercial rights for that territory. If the number of our addressable patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the treatment population is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved. Additionally, if we are not able to generate sufficient revenue from the sale of any approved products, we may never become profitable.

We may be unable to develop and commercialize Keyzilen®, Sonsuvi®, AM-125 or AM-201 or any other product candidate and, even if we do, may never achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of the Company and could impair our ability to raise capital, expand our business or continue our operations.

We expect that we will need substantial additional funding before we can expect to become profitable from sales of our products. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect our research and development expenses to remain significant in connection with our ongoing clinical development activities, particularly as we continue our ongoing trials of AM-125, may initiate new trials of Keyzilen® and Sonsuvi® and initiate pre-clinical and clinical development of other product candidates. We expect that our total operating expense in 2019 will be in the range of CHF 10.0 to 13.0 million. As of September 30, 2018, our cash and cash equivalents were CHF 5.3 million. We believe that our existing cash and cash equivalents will enable us to fund our operating expenses and capital expenditure requirements at least until the second quarter of 2019. Our assumptions may prove to be wrong, and we may have to use our capital resources sooner than we currently expect. If we are unable to raise capital when needed, we could be forced to delay, suspend, reduce or terminate our product development programs or commercialization efforts. Also, should we fail to raise sufficient funds to cover our operating expenditures for at least a 12 month period, we may no longer be considered a "going concern." The lack of a going concern assessment may negatively affect the valuation of the Company's investments in its subsidiaries and result in a revaluation of these holdings. Under Swiss law, should the Company's assets fall short of its liabilities as evidenced by the Company's standalone Swiss GAAP accounts, the board of directors will have to immediately take steps to restructure the business or if it fails to do, file for bankruptcy. If the board of directors fails to take appropriate action, under Swiss law, in case of such over-indebtedness, the auditors may, according to Swiss law, file for bankruptcy on the Company's behalf. Following the Redomestication, similar standards will apply under Bermuda law, and the board of directors will need to consider the interests of our creditors and take appropriate action to restructure the business if it appears that we are insolvent or likely to become insolvent. Our future funding requirements will depend on many factors, including but not limited to:

- the scope, rate of progress, results and cost of our clinical trials, nonclinical testing, and other related activities;

- the cost of manufacturing clinical supplies, and establishing commercial supplies, of our product candidates and any products that we may develop;
- the number and characteristics of product candidates that we pursue;
- the cost, timing, and outcomes of regulatory approvals;
- the cost and timing of establishing sales, marketing, and distribution capabilities; and
- the terms and timing of any collaborative, licensing, and other arrangements that we may establish, including any required milestone and royalty payments thereunder.

We expect that we will require additional funding to continue our ongoing clinical development activities and seek to obtain regulatory approval for, and commercialize, our product candidates. If we receive regulatory approval for any of our product candidates, and if we choose to not grant any licenses to partners, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution, depending on where we choose to commercialize. We also expect to continue to incur additional costs associated with operating as a public company. Additional funds may not be available on a timely basis, on favorable terms, or at all, and such funds, if raised, may not be sufficient to enable us to continue to implement our long-term business strategy. If we are not able to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

Raising additional capital may cause dilution to our shareholders, restrict our operations or require us to relinquish rights to our intellectual property or future revenue streams.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, grants, and license and development agreements in connection with any collaborations. We do not have any committed external source of funds. In the event we need to seek additional funds, we may raise additional capital through the sale of equity or convertible debt securities. In such an event, our shareholders' ownership interests will be diluted, and the terms of these new securities may include liquidation or other preferences that adversely affect our shareholders' rights as holders of our common shares. Debt financing, if available, may involve agreements, such as our term loan agreement with Hercules, that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our intellectual property or future revenue streams. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

We do not have a history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability.

Our operations to date have been limited to financing and staffing the Company, developing our technology and developing our product candidates. We have not yet demonstrated an ability to successfully complete large-scale, pivotal clinical trials, obtain marketing approvals, manufacture a commercial scale product or conduct sales and marketing activities necessary for successful product commercialization. Consequently, predictions about our future success or viability may not be as accurate as they could be if we had a history of successfully developing and commercializing pharmaceutical products.

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

We depend entirely on the success of Keyzilen®, Sonsuvi®, and AM-125 and AM-201, which are still in clinical development. If our clinical trials are unsuccessful, we do not obtain regulatory approval or we are unable to commercialize Keyzilen®, Sonsuvi®, AM-125 and AM-201, or we experience significant delays in doing so, our business, financial condition and results of operations will be materially adversely affected.

We currently have no products approved for sale and have invested a significant portion of our efforts and financial resources in the development of Keyzilen®, Sonsuvi®, AM-125 and AM-201, which are still in clinical development. Our ability to generate product revenues, which we do not expect will occur for at least the next few years, if ever, will depend heavily on successful clinical development, obtaining regulatory approval and eventual commercialization of these product candidates. We currently generate no revenues from sales of any drugs, and we may never be able to develop or commercialize a marketable drug. The success of Keyzilen®, Sonsuvi®, AM-125 and AM-201 and our other product candidates will depend on several factors, including the following:

- completing clinical trials that demonstrate the efficacy and safety of our product candidates;
- receiving marketing approvals from competent regulatory authorities;
- establishing commercial manufacturing capabilities;
- launching commercial sales, marketing and distribution operations;
- acceptance of our product candidates by patients, the medical community and third-party payors;
- a continued acceptable safety profile following approval;
- competing effectively with other therapies; and
- qualifying for, maintaining, enforcing and defending our intellectual property rights and claims.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize Keyzilen®, Sonsuvi®, AM-125 and AM-201, which would materially adversely affect our business, financial condition and results of operations.

Clinical drug development involves a lengthy and expensive process with uncertain timelines and uncertain outcomes, and results of earlier studies and trials may not be predictive of future trial results. If clinical trials of our product candidates are prolonged or delayed, we may be unable to obtain required regulatory approvals, and therefore be unable to commercialize our product candidates on a timely basis or at all.

To obtain the requisite regulatory approvals to market and sell any of our product candidates, we must demonstrate through extensive pre-clinical studies and clinical trials that our products are safe and effective in humans. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of pre-clinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. For example, positive results generated to date in clinical trials for our product candidates do not ensure that later clinical trials will demonstrate similar results. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through pre-clinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Our future clinical trial results may not be successful.

Clinical trials must be conducted in accordance with FDA, EMA and comparable foreign regulatory authorities' legal requirements, regulations or guidelines, and are subject to oversight by these governmental agencies and Institutional Review Boards, or IRBs, at the medical institutions where the clinical trials are conducted. In addition, clinical trials must be conducted with supplies of our product candidates produced under current good manufacturing practices, or cGMP, and other requirements. We depend on medical institutions and clinical research organizations, or CROs, to conduct our clinical trials in compliance with

current good clinical practice, or cGCP, standards. To the extent the CROs fail to enroll participants for our clinical trials, fail to conduct the trials to cGCP standards or are delayed for a significant time in the execution of trials, including achieving full enrollment, we may be affected by increased costs, program delays or both, which may harm our business.

To date, we have not completed all clinical trials required for the approval of any of our product candidates. Keyzilen® and Sonsuvi® are in Phase 3 clinical development and AM-125 is in Phase 2 and AM-201 is in Phase 1 clinical development.

The completion of clinical trials for our clinical product candidates may be delayed, suspended or terminated as a result of many factors, including but not limited to:

- the delay or refusal of regulators or IRBs to authorize us to commence a clinical trial at a prospective trial site and changes in regulatory requirements, policies and guidelines;
- delays or failure to reach agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- delays in patient enrollment and variability in the number and types of patients available for clinical trials;
- the inability to enroll a sufficient number of patients in trials to ensure adequate statistical power to detect statistically significant treatment effects;
- negative or inconclusive results, which may require us to conduct additional pre-clinical or clinical trials or to abandon projects that we expect to be promising;
- safety or tolerability concerns could cause us to suspend or terminate a trial if we find that the participants are being exposed to unacceptable health risks;
- regulators or IRBs requiring that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or safety concerns, among others;
- lower than anticipated retention rates of patients and volunteers in clinical trials;
- our CROs or clinical trial sites failing to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all, deviating from the protocol or dropping out of a trial;
- delays relating to adding new clinical trial sites;
- difficulty in maintaining contact with patients after treatment, resulting in incomplete data;
- errors in survey design, data collection and translation;
- delays in establishing the appropriate dosage levels;
- the quality or stability of the product candidate falling below acceptable standards;
- the inability to produce or obtain sufficient quantities of the product candidate to complete clinical trials; and
- exceeding budgeted costs due to difficulty in accurately predicting costs associated with clinical trials.

Any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, financial condition and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

Positive or timely results from pre-clinical or early-stage trials do not ensure positive or timely results in late-stage clinical trials or product approval by the FDA, the EMA or comparable foreign regulatory authorities. Product candidates that show positive pre-clinical or early clinical results may not show sufficient safety or efficacy in later stage clinical trials and therefore may fail to obtain regulatory approvals. For example, although Keyzilen® achieved favorable results in our Phase 2 efficacy trial, in August 2016, we announced that the Phase 3 TACTT2 clinical trial of Keyzilen® did not meet its two co-primary efficacy endpoints of statistically significant changes in tinnitus loudness and tinnitus burden compared to placebo. On March 13, 2018, we announced preliminary top-line data from the TACTT3 trial which indicated that the study had not met its primary efficacy endpoint of a statistically significant improvement in the Tinnitus Functional Score from baseline to Day 84 in the active treated group compared to placebo either in the overall population or in the otitis media subpopulation. On May 15, 2018, we announced that further investigation of the trial's outcomes confirmed these preliminary results.

Also, pre-clinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in pre-clinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. The FDA, the EMA and comparable foreign regulatory authorities have substantial discretion in the approval process and in determining when or whether regulatory approval will be obtained for any of our product candidates. Even if we believe the data collected from clinical trials of our product candidates are promising, such data may not be sufficient to support approval by the FDA, the EMA or any other regulatory authority.

In some instances, there can be significant variability in safety and/or efficacy results between different trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, adherence to the dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. In the case of our late-stage clinical product candidates, results may differ in general on the basis of the larger number of clinical trial sites and additional countries and languages involved in Phase 3 clinical trials.

In the case of Keyzilen®, our endpoints in Phase 3 clinical trials are based on patient reported outcomes, or PROs, some of which were captured daily from trial participants with electronic diaries. Based on insights from our analysis of the TACTT2 and TACTT3 trials, we believe the high frequency of tinnitus loudness ratings over an extended period of time may have caused a number of patients to excessively focus on their tinnitus symptoms, thereby influencing the measured outcome. In addition, the daily reporting requirements may have led to rating fatigue and a loss of accuracy and reliability of the data that were entered. In the previous clinical trials with Keyzilen® we had collected these PROs only during study visits, i.e. much less frequently. Under the SPA with the FDA we agreed to increase the rating frequency.

In the case of Sonsuvi®, we are evaluating the safety and efficacy in an idiopathic condition which implies a considerable heterogeneity in the etiology and natural history of the condition. In addition, we are dealing with a limited availability of detailed and reliable data relating to the natural history of acute hearing loss, which implies substantial uncertainty with regards to the design of clinical trials, e.g. for determining the number of patients required for statistical testing or the size of the expected treatment effect. For example, a Phase 2 clinical trial with Sonsuvi® showed a strong relationship between the level or severity of initial hearing loss and the size of the treatment effect for active-treated patients compared to placebo-treated patients. Whereas a high spontaneous recovery rate and no treatment effects were observed in patients with mild to moderate hearing loss at baseline, lower spontaneous recovery and meaningful treatment effects were observed in patients with severe to profound hearing loss. Accordingly, enrollment into the Phase 3 trials HEALOS and ASSENT was restricted to patients with severe-profound hearing loss at baseline. On November 28, 2017, we announced that the HEALOS Phase 3 clinical trial that investigated Sonsuvi® in the treatment of acute inner ear hearing loss did not meet the primary efficacy endpoint of a statistically significant improvement in hearing from baseline to Day 28 compared to placebo for either active treatment groups in the overall study population. However, a post-hoc analysis of the subpopulation with profound acute hearing loss (PTA $\geq$ 90 dB at baseline in accordance with a commonly used classification of hearing loss severity) revealed a clinically meaningful and nominally significant improvement in the Sonsuvi® 0.4 mg/mL treatment group. Accordingly, in HEALOS we found confirmation about the relationship between severity of hearing loss and the size of therapeutic effects; however, such therapeutic effects were not observed in the subgroup of patients with severe initial hearing

loss but rather, unlike in the Phase 2 trial, only in the subgroup with profound initial hearing loss. We understand from animal studies that the pharmacological target for Sonsuvi® is only activated in case of severe acute cochlear injury; however, activation of this target cannot be determined in humans, and we have to rely on the measurement of hearing loss for assessing the severity of injury.

Based on the results from the HEALOS clinical trial, we submitted the design of a new pivotal trial with AM-111 0.4 mg/mL in patients suffering from acute profound hearing loss to the EMA and subsequently also to the FDA for review. Through a Protocol Assistance procedure the EMA endorsed the proposed trial design, choice of efficacy and safety endpoints, as well as the statistical methodology. In a Type C meeting with written responses, the proposed choice of primary and secondary efficacy endpoints, the safety endpoints, as well as the planned sample size and statistical methodology were also endorsed by the FDA. Orphan drug designation for AM-111 was granted by the FDA and EMA for the treatment of acute sensorineural hearing loss, or ASNHL, an umbrella term that comprises hearing loss from acute acoustic trauma, or AAT, surgery-induced trauma, or ISSNHL. We estimate ISSNHL to be the largest of the three subgroups. The broader, more general designation of ASNHL is based on the common pathophysiologic pathway shared by the three subgroups. Although we expect to obtain regulatory approval for the entire indication of ASNHL based on confirmatory efficacy and safety data that covers only one or two rather than all three of the subgroups, there can be no assurance that regulatory agencies will concur with this assumption at the time of the marketing approval procedure. In that case, it may not be sufficient to conduct trials in the subgroup of ISSNHL, as is currently planned to gain the indication for ASNHL.

If we are required to conduct additional clinical trials or other testing of Keyzilen®, Sonsuvi®, AM-125, AM-201 or any other product candidate that we develop beyond the trials and testing that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are unfavorable or are only modestly favorable or if there are safety concerns associated with Keyzilen®, Sonsuvi® or our other product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;
- be subject to additional post-marketing testing or other requirements; or
- remove the product from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in testing or marketing approvals or if we are required to conduct additional clinical trials or other testing of Keyzilen®, Sonsuvi®, AM-125 or AM-201 beyond the trials and testing that we currently contemplate and we may be required to obtain additional funds to complete such additional clinical trials. We cannot assure you that our clinical trials will begin as planned or be completed on schedule, if at all, or that we will not need to restructure our trials after they have begun. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do or shorten any periods during which we have the exclusive right to commercialize our product candidates, which may harm our business and results of operations. In addition, some of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of regulatory approval of Keyzilen®, Sonsuvi®, AM-125, AM-201 or any other product candidate.

If serious adverse, undesirable or unacceptable side effects are identified during the development of our product candidates or following approval, if any, we may need to abandon our development of such product candidates, the commercial profile of any approved label may be limited, or we may be subject to other significant negative consequences following marketing approval, if any.

If our product candidates are associated with serious adverse, undesirable or unacceptable side effects, we may need to abandon their development or limit development to certain uses or sub-populations in which such side effects are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in pre-clinical or early-stage testing have later been found to cause side effects that restricted their use and prevented further development of the compound for larger indications.

In our clinical trials of Keyzilen® and Sonsuvi® to date, adverse events have included procedure-related transient changes in tinnitus loudness, muffled hearing, ear discomfort or pain, incision site complications and middle ear infections. A limited number of serious adverse events were observed (in 1.2 to 2.5% of patients enrolled in the Keyzilen® trials and in 2.7 to 4.5% of patients in the Sonsuvi® trials); all (Keyzilen®) or most (Sonsuvi®) were considered unrelated or unlikely related to the treatment. In the two Phase 1 trials with intranasal betahistine, adverse events included transient and dose-dependent nasal congestion or discomfort. Occurrence of serious procedure- or treatment-related side effects could impede clinical trial enrollment and receipt of marketing approval from the FDA, the EMA and comparable foreign regulatory authorities. They could also adversely affect physician or patient acceptance of our product candidates.

Additionally, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients; and
- our reputation and physician or patient acceptance of our products may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

We depend on enrollment of patients in our clinical trials for our product candidates. If we are unable to enroll patients in our clinical trials, our research and development efforts could be materially adversely affected.

Successful and timely completion of clinical trials will require that we enroll a sufficient number of patient candidates. Trials may be subject to delays as a result of patient enrollment taking longer than anticipated or patient withdrawal. Patient enrollment depends on many factors, including the size and nature of the patient population, eligibility criteria for the trial, the proximity of patients to clinical sites, the design of the clinical protocol, the availability of competing clinical trials, the availability of new drugs approved for the indication the clinical trial is investigating, and clinicians' and patients' perceptions as to the potential advantages of the drug being studied in relation to other available therapies.

The specific target population of patients and therapeutic time windows may make it difficult for us to enroll enough patients to complete our clinical trials in a timely and cost-effective manner. Delays in the completion of any clinical trial of our product candidates will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate revenue. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

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

We are exposed to potential product liability and professional indemnity risks that are inherent in the research, development, manufacturing, marketing and use of pharmaceutical products. Currently, we have no products that have been approved for commercial sale; however, the current and future use of product candidates by us in clinical trials, and the sale of any approved products in the future, may expose us to liability claims. These claims might be made by patients that use the product, healthcare providers, pharmaceutical companies or others selling such products. Any claims against us, regardless of their merit, could be difficult and costly to defend and could materially adversely affect the market for our product candidates or any prospects for commercialization of our product candidates.

Although the clinical trial process is designed to identify and assess potential side effects, it is always possible that a drug, even after regulatory approval, may exhibit unforeseen side effects. If any of our product candidates were to cause adverse side effects during clinical trials or after approval of the product candidate, we may be exposed to substantial liabilities. Physicians and patients may not comply with any warnings that identify known potential adverse effects and patients who should not use our product candidates.

We purchase liability insurance in connection with each of our clinical trials. It is possible that our liabilities could exceed our insurance coverage. We intend to expand our insurance coverage to include the sale of commercial products if we obtain marketing approval for any of our product candidates. However, we may not be able to maintain insurance coverage at a reasonable cost or obtain insurance coverage that will be adequate to satisfy any liability that may arise. If a successful product liability claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, our assets may not be sufficient to cover such claims and our business operations could be impaired.

Should any of the events described above occur, this could have a material adverse effect on our business, financial condition and results of operations.

We have obtained orphan drug designation for Sonsuvi® for the treatment of ASNHL from the FDA and the EMA, and we may rely on obtaining and maintaining orphan drug exclusivity for Sonsuvi®, if approved. Orphan drug designation may not ensure that we will enjoy market exclusivity in a particular market, and if we fail to obtain or maintain orphan drug exclusivity for Sonsuvi®, we may be subject to earlier competition and our potential revenue will be reduced.

Sonsuvi® has been granted orphan drug designation for the treatment of ASNHL by the FDA and EMA. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is intended to treat a rare disease or condition, defined as a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, the EMA's Committee for Orphan Medicinal Products, or COMP, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the European Union. Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biological product or where there is no satisfactory method of diagnosis, prevention, or treatment, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity. In the European Union, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity following drug or biological product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Even though we have obtained orphan drug designation for Sonsuvi® for the treatment of ASNHL in the United States and Europe, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing pharmaceutical products. Further, even if we obtain orphan drug designation for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same condition. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

The orphan drug designation for Sonsuvi® relates to ASNHL, an umbrella term comprising AAT, ISSNHL and surgery-induced trauma based on a common pathophysiologic pathway. Our Phase 3 late-stage program enrolled patients suffering from ISSNHL, which represent the largest of the three ASNHL subgroups.

Due to our limited resources and access to capital, we must and have in the past decided to prioritize development of certain product candidates; these decisions may prove to have been wrong and may adversely affect our revenues.

Because we have limited resources and access to capital to fund our operations, we must decide which product candidates to pursue and the amount of resources to allocate to each. As such, we have been primarily focused on the development of Keyzilen®, Sonsuvi®, AM-125 and AM-201 for the treatment of acute inner ear tinnitus, acute inner ear hearing loss, vertigo and antipsychotic-induced weight gain, respectively. Our decisions concerning the allocation of research, collaboration, management and financial resources toward particular compounds, product candidates or therapeutic areas may not lead to the development of viable commercial products and may divert resources away from better opportunities. Similarly, our potential decisions to delay, terminate or collaborate with third parties in respect of certain product development programs may also prove not to be optimal and could cause us to miss valuable opportunities. If we make incorrect determinations regarding the market potential of our product candidates or misread trends in the biopharmaceutical industry, in particular for inner ear disorders, our business, financial condition and results of operations could be materially adversely affected.

Our research and development activities could be affected or delayed as a result of possible restrictions on animal testing.

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

Risks Related to Regulatory Approval of Our Product Candidates

We cannot give any assurance that any of our product candidates will receive regulatory approval, which is necessary before they can be commercialized.

Our future success is dependent on our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize one or more product candidates. We currently have two lead clinical-stage product candidates, (i) Keyzilen® (AM-101), which is being developed for the treatment of acute inner ear tinnitus and (ii) Sonsuvi® (AM-111), being developed for the treatment of acute inner ear hearing loss. Additionally, we have one product candidate, AM-125, in Phase II clinical development, and another, AM-201, in Phase I clinical development. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA, EMA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates.

Although certain of our employees have prior experience with submitting marketing applications to the FDA, EMA or comparable foreign regulatory authorities, we as a company have not submitted such applications for our product candidates. We cannot be certain that any of our product candidates will be successful in clinical trials or receive regulatory approval. Applications for our product candidates could fail to receive regulatory approval for many reasons, including but not limited to the following:

- the FDA, EMA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- the population studied in the clinical program may not be sufficiently broad or representative to assure safety in the full population for which we seek approval;

- the FDA, EMA or comparable foreign regulatory authorities may disagree with our interpretation of data from nonclinical trials or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of a new drug application, or NDA, or other submission or to obtain regulatory approval in the United States or elsewhere;
- we may be unable to demonstrate to the FDA, EMA or comparable foreign regulatory authorities that a product candidate's risk-benefit ratio for its proposed indication is acceptable;
- the FDA, EMA or other regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications, or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA, EMA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

In addition, no product for the treatment of acute inner ear tinnitus, acute inner ear hearing loss or antipsychotic-induced weight gain has been approved by the FDA or the EMA. Accordingly, our current product candidates or any of our other future product candidates could take a significantly longer time to gain regulatory approval than expected or may never gain regulatory approval. This could delay or eliminate any potential product revenue by delaying or terminating the potential commercialization of our product candidates.

We generally plan to seek regulatory approval to commercialize our product candidates in the United States, the European Union and in additional foreign countries where we have commercial rights. To obtain regulatory approval in other countries, we must comply with numerous and varying regulatory requirements of such other countries regarding safety, efficacy, chemistry, manufacturing and controls, clinical trials, commercial sales, pricing, and distribution of our product candidates. Even if we are successful in obtaining approval in one jurisdiction, we cannot ensure that we will obtain approval in any other jurisdictions. Failure to obtain marketing authorization for our product candidates will result in our being unable to market and sell such products, which would materially adversely affect our business, financial conditional and results of operations. If we fail to obtain approval in any jurisdiction, the geographic market for our product candidates could be limited. Similarly, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates.

Because we are developing therapies for which there is little clinical experience and, in some cases, using new endpoints, there is more risk that the outcome of our clinical trials will not be favorable. Even if the results of our trials are favorable, there is risk that they will not be acceptable to regulators or physicians.

There are currently no drugs with proven efficacy for acute inner ear tinnitus or acute inner ear hearing loss. In addition, there has been limited historical clinical trial experience generally for the development of drugs to treat these conditions. Regulatory authorities in the United States and European Union have not issued definitive guidance as to how to measure the efficacy of treatments for acute inner ear tinnitus or acute inner ear hearing loss, and regulators have not yet established what is required to be demonstrated in a clinical trial in order to signify a clinically meaningful result and/or obtain marketing approval. We designed our Phase 3 trials for Keyzilen® and Sonsuvi® to include endpoints that we believe are clinically justified and meaningful. Specifically, with regard to Keyzilen®, the EMA indicated that a statistically significant improvement in tinnitus loudness that is supported by several secondary variables would demonstrate a clinically meaningful result. The FDA indicated that an improvement in tinnitus loudness supported by a co-primary efficacy point, such as the TFI questionnaire, would be clinically meaningful.

With regard to Sonsuvi®, the FDA and EMA have indicated that a 10 dB improvement in hearing thresholds is clinically significant, in line with clinical practice. However, no product has been approved for marketing based upon such guidance and we cannot be certain that Sonsuvi® will be approved even if it were to demonstrate such result in further Phase 3 trials.

Whereas various balance tests such as the tandem Romberg or standing on foam tests or other objective measures such as nystagmography or head impulse tests are widely used in the diagnosis and management of vertigo, there is no universally recognized definition of the clinical meaningfulness of outcomes, and regulatory authorities have not issued guidelines for demonstrating efficacy for drug-based treatments such as AM-125. Therefore we cannot be certain that AM-125 will be approved even if it were to show statistically significant improvements in these tests.

Some of our conclusions regarding the potential efficacy of Sonsuvi® in our completed HEALOS clinical trial for the treatment of ASNHL in the subgroup of patients with profound acute hearing loss is based on retrospective analyses of the results, which are generally considered less reliable indicators of efficacy than pre-specified analyses.

After determining that we did not achieve the primary efficacy endpoint in our completed HEALOS clinical trial of Sonsuvi® for the treatment of ASNHL, we performed retrospective analyses that we believe show treatment effects on the magnitude of hearing recovery in favor of Sonsuvi® in case of profound hearing loss at baseline. Although we believe that these additional analyses were warranted, a retrospective analysis performed after unblinding trial results can result in the introduction of bias if the analysis is inappropriately tailored or influenced by knowledge of the data and actual results. In particular, the analysis that resulted in a clinically meaningful effect being observed in active-treated patients who suffered from profound acute hearing loss poses greater risk of bias as such subgroup was not pre-specified in the trial design, notwithstanding that we applied a commonly used definition of profound hearing loss.

Because of these limitations, regulatory authorities typically give greatest weight to results from pre-specified analyses and less weight to results from post-hoc, retrospective analyses. According to discussions with the EMA and FDA, the therapeutic benefits that were observed in the HEALOS subgroup of profound acute hearing loss will need to be confirmed prospectively in one or more additional Phase 3 trials in order to gain regulatory market approval. However, there is no guarantee that we will ever receive such regulatory approval.

Safety issues with isomers of our product candidates or with approved products of third parties that are similar to our product candidates, could delay or prevent the regulatory approval process or result in restrictions on labeling.

Discovery of previously unknown problems, or increased focus on a known problem, with an approved product may result in restrictions on its permissible uses, including withdrawal of the medicine from the market. Esketamine and betahistine, the active pharmaceutical ingredients, or APIs, of Keyzilen® and AM-125, may be affected by the safety of the drugs related to them. Although both APIs have been used successfully in patients for many years, newly observed toxicities or worsening of known toxicities, in pre-clinical studies of, or in patients receiving, Esketamine, the racemate Ketamine or betahistine, or reconsideration of known toxicities of these APIs in the setting of new indications, could result in increased regulatory scrutiny of Keyzilen® or AM-125. For example, Ketamine is regulated by the Drug Enforcement Administration, or DEA, under the Controlled Substances Act, or CSA, as a Schedule III drug. DEA scheduling is a separate process that can delay when a drug may become available to patients beyond a NDA approval date, and the timing and outcome of such DEA process is uncertain. Although we have observed no abuse liability associated with Keyzilen® to date, if Keyzilen® were to be scheduled under the CSA, such scheduling could negatively impact the ability or willingness of physicians to prescribe Keyzilen® and our ability to commercialize it.

Substantial additional data may need to be generated in order to obtain marketing approval for AM-125.

Oral betahistine has been in clinical use for several decades and is reported to be currently marketed in 115 countries world-wide. However, in the United States oral betahistine is not approved since the FDA revoked the drug product's marketing authorization in the early 1970s over issues with unsubstantiated information about some patients in the efficacy studies upon which approval had been based. Given the absence of an approved betahistine drug product in the United States and to the extent that existing data may not be deemed sufficient, the FDA may require a full development package for AM-125.

Furthermore, additional data will be required for the specific formulation of AM-125 and the intranasal administration route. Since intranasal delivery of betahistine has the potential to result in substantially higher systemic exposures as measured by concentrations in blood plasma compared to oral delivery, existing safety assessments conducted with or for the approved drug product may not be sufficient. In addition, some of these assessments were performed a long time ago and may not be in line with current regulations and guidelines. Therefore the scope of our development program for AM-125 may ultimately not be much smaller than one for new chemical entities.

Even if our product candidates obtain regulatory approval, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

If marketing authorization is obtained for any of our product candidates, the product will remain subject to continual regulatory review and therefore authorization could be subsequently withdrawn or restricted. Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials and surveillance to monitor the safety and efficacy of the product candidate. In addition, if the FDA or a comparable foreign regulatory authority approves any of our product candidates, we will be subject to ongoing regulatory obligations and oversight by regulatory authorities, including with respect to the manufacturing processes, labeling, packing, distribution, adverse event reporting, storage, advertising and marketing restrictions, and recordkeeping and, potentially, other post-marketing obligations, all of which may result in significant expense and limit our ability to commercialize such products. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMPs, cGDPs and cGCPs for any clinical trials that we conduct post-approval. In the European Union, the marketing authorization holder has to operate a pharmacovigilance system which conforms with and is equivalent to the respective Member State's pharmacovigilance system, requiring him to evaluate all information scientifically, to consider options for risk minimization and prevention and to take appropriate measures as necessary. As part of this system, we will have to, inter alia, have a qualified person responsible for pharmacovigilance, maintain a pharmacovigilance system master file, operate a risk management system for each medicinal product, monitor the outcome of risk minimization measures, and update continuously all pharmacovigilance data to update the risk assessment.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market, or voluntary or mandatory product recalls;
- fines, warning letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; and
- injunctions or the imposition of civil or criminal penalties.

If any of these events occurs, our ability to sell such product may be impaired, and we may incur substantial additional expense to comply with regulatory requirements, which could materially adversely affect our business, financial condition and results of operations. The FDA's or any other regulatory authority's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained, which would adversely affect our business, prospects and ability to achieve or sustain profitability.

Enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and may affect the prices we may set.

In the United States and the European Union, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system. These changes could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any products for which we obtain marketing approval.

For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the Health Care Reform Law was enacted, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for health care and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The Health Care Reform Law, among other things, increased rebates a manufacturer must pay to the Medicaid program, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, established a Medicare Part D coverage gap discount program, in which manufacturers must provide 50% point-of-sale discounts on products covered under Part D and implemented payment system reforms including a national pilot program on payment bundling to encourage hospitals, physicians and other providers to improve the coordination, quality and efficiency of certain healthcare services through bundled payment models. Further, the law imposed a significant annual fee on companies that manufacture or import branded prescription drug products, expanded eligibility criteria for Medicaid programs, and created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research. Substantial provisions affecting compliance were enacted, which may affect our business practices with health care practitioners. Continued pressure on pharmaceutical pricing is expected and may also increase our regulatory burdens and operating costs.

Other legislative changes have been proposed and adopted in the United States since the Health Care Reform Law was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2025 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other health care funding, which could have a material adverse effect on our customers and accordingly, our financial operations. Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing by requiring drug companies to notify insurers and government regulators of price increases and provide an explanation of the reasons for the increase, reduce the out-of-pocket cost of prescription drug, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. Moreover, U.S. President Donald Trump has discussed the need for federal legislation, regulation or Executive Order to regulate the prices of medicines.

Because of the continued uncertainty about the implementation of the Health Care Reform Law, including the potential for further legal challenges or repeal of that legislation, we cannot quantify or predict with any certainty the likely impact of the Health Care Reform Law or its repeal on our business model, prospects, financial condition or results of operations, in particular on the pricing, coverage or reimbursement of any of our product candidates that may receive marketing approval. We also anticipate that Congress, state legislatures, and third-party payors may continue to review and assess alternative healthcare delivery and payment systems and may in the future propose and adopt legislation or policy changes or implementations effecting additional fundamental changes in the healthcare delivery system. We

cannot assure you as to the ultimate content, timing, or effect of changes, nor is it possible at this time to estimate the impact of any such potential legislation.

In the European Union, a new clinical trial regulation centralizes clinical trial approval, which eliminates redundancy, but in some cases this may extend timelines for clinical trial approvals due to potentially longer wait times. The regulation requires specific consents for use of data in research which, among other measures, may increase the costs and timelines for our product development efforts. The regulation also provides an obligation for clinical trial sponsors to make summaries of all trial results, accompanied by a summary understandable to laypersons, as well as the clinical trial report publicly available in a new database. Beyond this obligation, the EMA adopted a new "Agency policy on publication of clinical data" (in force since January 1, 2015) based on which the EMA makes available to the public all clinical trials submitted with the EMA as well as raw data results ("individual patient data"). These publication requirements can conflict with legitimate secrecy interests of the sponsors and may lead to valuable clinical trial data falling into the public domain.

On June 23, 2016, the UK public voted in a referendum to leave the European Union. The UK government subsequently announced its intention to serve notice of withdrawal from the European Union no later than March 2017. As a consequence of such withdrawal notice, EU law will cease to apply to the UK from the date of entry into force of a withdrawal agreement, or two years after UK's submission of the withdrawal notification. As a result, the UK is likely to remain within the European Union for at least the next two years, and, therefore there will likely be no major legal implications for the life sciences sector in the short term. In the long term, however, the effects may be more severe, in particular if the UK cannot agree the terms of a continued close association with the European Union and/or chooses not to incorporate existing EU rules into national law and/or to no longer align themselves with European law. The administrative burden for pharmaceutical companies could increase significantly because regulatory requirements, for example clinical trial authorizations and marketing authorization applications, may need to be fulfilled under a new and different legal framework for the UK. Existing marketing authorizations granted in the European Union under the centralized procedure prior to the exit may potentially not be recognized anymore by the UK.

Austerity measures in certain European nations may also affect the prices we are able to seek if our products are approved, as discussed below.

Both in the United States and in the European Union, legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We do not know whether additional legislative changes will be enacted, or whether the regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be.

Our relationships with customers and payors may be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which, if violated, could expose us to criminal sanctions, civil penalties, exclusion from government healthcare programs, contractual damages, reputational harm and diminished profits and future earnings, among other penalties.

Healthcare providers, payors and others play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, primarily in the United States, that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products for which we obtain marketing approval. Restrictions under applicable U.S. healthcare laws and regulations, include the following:

- the U.S. healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under U.S. government healthcare programs such as Medicare and Medicaid;

- the U.S. False Claims Act imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the U.S. government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

- the U.S. Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the transparency requirements under the Health Care Reform Law require manufacturers of drugs, devices, biologics and medical supplies to report to the U.S. Department of Health and Human Services information related to payments and other transfers of value made by such manufacturers to physicians and teaching hospitals, and ownership and investment interests held by physicians or their immediate family members; and

- analogous laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures.

Similar laws exist in other jurisdictions.

In the European Union, there is currently no central European anti-bribery or similar legislation. However, more and more EU member states as well as life sciences industry associations are enacting increasingly specific anti-bribery rules for the healthcare sector which are as severe and sometimes even more severe than in the United States. Germany, for example, has recently adopted new criminal provisions dealing with granting benefits to healthcare professionals. This new law has increased the legal restrictions as well as the legal scrutiny for the collaboration and contractual relationships between the pharmaceutical industry and its customers.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available under the U.S. federal Anti-Kickback Statute, it is possible that some of our future business activities could be subject to challenge under one or more of such laws. In addition, recent health care reform legislation has strengthened these laws. For example, the Health Care Reform Law, among other things, amends the intent requirement of the federal anti-kickback and criminal healthcare fraud statutes. A person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it. Moreover, the Health Care Reform Law provides that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from U.S. government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business with are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

Risks Related to Commercialization of Our Product Candidates

We operate in highly competitive and rapidly changing industries, which may result in others discovering, developing or commercializing competing products before or more successfully than we do.

The biopharmaceutical and pharmaceutical industries are highly competitive and subject to significant and rapid technological change. Our success is highly dependent on our ability to discover, develop and obtain marketing approval for new and innovative products on a cost-effective basis and to market them successfully. In doing so, we face and will continue to face intense competition from a variety of businesses, including large, fully integrated pharmaceutical companies, specialty pharmaceutical companies and biopharmaceutical companies, academic institutions, government agencies and other private and public research institutions in Europe, the United States and other jurisdictions. These organizations may have significantly greater resources than we do and conduct similar research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and marketing of products that compete with our product candidates.

We believe that our key competitors are Otonomy, Inc., or Otonomy, Sound Pharmaceuticals, Inc., or Sound Pharma, and Sensorion SA, or Sensorion. In October 2013, Otonomy announced the launch of a development program for the treatment of tinnitus, OTO-311, which is based on the NMDA receptor antagonist gacyclidine and may directly compete with our Keyzilen® product candidate. According to a recent public filing, Otonomy intends to develop a polymer-based formulation of gacyclidine that will provide a full course of treatment from a single intratympanic injection. Following a Phase 1 trial, Otonomy made adjustments to the formulation, resulting in product candidate OTO-313, which the company plans to evaluate in a Phase 1/2 trial starting in 2019. OTO-313's competitive strength will ultimately depend on the demonstration of clinical efficacy and safety and its comparison with Keyzilen®. Otonomy is also developing OTO-104, which is a polymer-based formulation of dexamethasone for intratympanic treatment of vertigo in Ménière's disease. In Phase 3 of clinical development, OTO-104 showed no treatment effects in a North American study, but showed treatment effects in a European study, which had been terminated early. In March 2018 the company announced its intention to conduct another Phase 3 study with OTO-104. If Otonomy's drug product is approved prior to AM-125, we will have to compete against it in the treatment of vertigo in Ménière's disease. In addition, OTO-104 is being evaluated by Otonomy for the treatment of certain types of hearing loss and may compete against Sonsuvi®.

In June 2006, Sound Pharma began clinical testing of an oral treatment for hearing loss (SPI-1005, ebselen). Its active substance mimics and prompts production of the glutathione peroxidase enzyme. In February 2014, Sound Pharma announced positive outcomes from a placebo-controlled Phase 2 clinical trial with SPI-1005 in the prevention of temporary inner ear hearing loss from listening to loud music with a mobile digital media player. Although Sonsuvi® targets permanent rather than transient hearing loss, SPI-1005 may become competing products if Sound Pharma seeks and manages to demonstrate clinical efficacy also in the prevention and treatment of permanent inner ear hearing loss.

Sensorion is developing SENS-401, a 5-HT3 antagonist with anti-inflammatory properties, for the oral treatment of sudden sensorineural hearing loss. The company is initiating a Phase 2 clinical trial with SENS-401 in the treatment of sudden sensorineural hearing loss. Sensorion is also developing SENS-111, a histamine H4 receptor antagonist, for the oral treatment of acute vertigo crises and in 2017 initiated a Phase 2 trial to enroll patients with acute unilateral vestibulopathy. According to Sensorion, this trial will conclude in the second half of 2019. If successful, SENS-401 may compete against Sonsuvi®, and SENS-111 may compete against AM-125.

There are several companies developing treatments for hearing loss. Strekin AG, a privately held Swiss company, announced in April 2016 that it plans to develop STR001, an agonist of the peroxisome proliferator, for surgery induced hearing loss and that it commenced a Phase 2 program in Germany and France. Nordmark, a German company, is developing Ancrod, the biologically active substance from the venom of the Malayan Pit Viper (*Calloselasma rhodostoma*), for the treatment of sudden sensorineural hearing loss and has initiated Phase 2 program. Both, STR001 and Ancrod have the potential to compete with Sonsuvi®.

There exist a variety of drug products that are licensed or used off-label for the treatment of vestibular disorders and Ménière's disease, including steroids, diuretics, anti-emetics or anti-nausea medications. In many countries outside the United States, oral betahistine is the standard of care and licensed for the treatment of Ménière's disease and vestibular vertigo. Although, we expect that AM-125 will offer benefits over oral betahistine due to the ability to bypass the strong first-pass metabolism associated with oral intake and provide for a higher bioavailability and avoid gastric side effects, it may take time to change prescribing and usage patterns in favor of the newer product.

The highly competitive nature of and rapid technological changes in the biotechnology and pharmaceutical industries could render our product candidates or our technology obsolete or non-competitive. Our competitors may, among other things:

- develop and commercialize products that are safer, more effective, less expensive, or more convenient or easier to administer;
- obtain quicker regulatory approval;
- establish superior proprietary positions;
- have access to more manufacturing capacity;
- implement more effective approaches to sales and marketing; or
- form more advantageous strategic alliances.

Should any of these occur, our business, financial condition and results of operations could be materially adversely affected.

The successful commercialization of our product candidates will depend in part on the extent to which governmental authorities and health insurers establish adequate coverage and reimbursement levels and pricing policies.

The successful commercialization of Keyzilen®, Sonsuvi®, AM-125, AM-201 or our other product candidates will depend, in part, on the extent to which coverage and reimbursement for our products or procedures using our products will be available from government and health administration authorities, private health insurers and other third-party payors. To manage healthcare costs, many governments and third-party payors increasingly scrutinize the pricing of new technologies and require greater levels of evidence of favorable clinical outcomes and cost-effectiveness before extending coverage. In light of such challenges to prices and increasing levels of evidence of the benefits and clinical outcomes of new technologies, we cannot be sure that coverage will be available for Keyzilen®, Sonsuvi®, AM-125 or any other product candidate that we commercialize and, if available, that the reimbursement rates will be adequate.

Our customers, including hospitals, physicians and other healthcare providers that purchase certain injectable drugs administered during a procedure, such as our product candidates, generally rely on third-party payors to pay for all or part of the costs and fees associated with the drug and the procedures administering the drug. These third-party payors may pay separately for the drug or may bundle or otherwise include the costs of the drug in the payment for the procedure. We are unable to predict at this time whether our product candidates, if approved, will be eligible for such separate payments. Nor can we predict at this time the adequacy of payments, whether made separately for the drug and procedure or with a bundled or otherwise aggregate payment amount for the drug and procedure. In addition, obtaining and maintaining adequate coverage and reimbursement status is time-consuming and costly.

Third-party payors may deny coverage and reimbursement status altogether of a given drug product, or cover the product but may also establish prices at levels that are too low to enable us to realize an appropriate return on our investment in product development. Because the rules and regulations regarding coverage and reimbursement change frequently, in some cases at short notice, even when there is favorable coverage and reimbursement, future changes may occur that adversely impact the favorable status. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States.

The unavailability or inadequacy of third-party coverage and reimbursement could have a material adverse effect on the market acceptance of our product candidates and the future revenues we may expect to receive from those products. In addition, we are unable to predict what additional legislation or regulation relating to the healthcare industry or third-party coverage and reimbursement may be enacted in the future, or what effect such legislation or regulation would have on our business.

Our products may not gain market acceptance, in which case we may not be able to generate product revenues, which will materially adversely affect our business, financial condition and results of operations.

Even if the FDA, the EMA or other regulatory authority approves the marketing of any product candidates that we develop, physicians, healthcare providers, patients or the medical community may not accept or use them. Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If Keyzilen®, Sonsuvi®, AM-125 or any other product candidate that we develop does not achieve an adequate level of acceptance, we may not generate significant product revenues or any profits from operations. The degree of market acceptance of Keyzilen®, Sonsuvi®, AM-125 or any of our product candidates that is approved for commercial sale will depend on a variety of factors, including:

- how clinicians and potential patients perceive our novel products;
- the timing of market introduction;
- the number and clinical profile of competing products;
- our ability to provide acceptable evidence of safety and efficacy;
- the prevalence and severity of any side effects;
- relative convenience and ease of administration, particularly as Keyzilen® and Sonsuvi® have to be administered by an ear, nose, throat physician, and in case of Keyzilen® the procedure has to be repeated for a total of three times;
- cost-effectiveness;
- patient diagnostics and screening infrastructure in each market, particularly as Keyzilen®, Sonsuvi® and AM-125, are being developed for the treatment of acute inner ear disorders and are thus dependent on a relatively rapid diagnosis and dosing process;
- marketing and distribution support;
- availability of coverage, reimbursement and adequate payment from health maintenance organizations and other third-party payors, both public and private; and
- other potential advantages over alternative treatment methods.

If our product candidates fail to gain market acceptance, this will have a material adverse impact on our ability to generate revenues to provide a satisfactory, or any, return on our investments. Even if some products achieve market acceptance, the market may prove not to be large enough to allow us to generate significant revenues.

In addition, the potential market opportunity of Keyzilen®, Sonsuvi®, AM-125 and AM-201 are difficult to precisely estimate. Our estimates of the potential market opportunity are predicated on several key assumptions such as industry knowledge and publications, third-party research reports and other surveys. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain and the reasonableness of these assumptions could not have been assessed by an independent source in every detail. If any of the assumptions proves to be inaccurate, then the actual market for Keyzilen®, Sonsuvi®, AM-125 and AM-201 could be smaller than our estimates of the potential market opportunity. If the actual market for Keyzilen®, Sonsuvi®, AM-125 and AM-201 is smaller than we expect, or if the products fail to achieve an adequate level of acceptance by physicians, health care payors and patients, our product revenue may be limited and it may be more difficult for us to achieve or maintain profitability.

We have never commercialized a product candidate before and may lack the necessary expertise, personnel and resources to successfully commercialize our products on our own or together with suitable partners.

We have never commercialized a product candidate, and we currently have no sales force, marketing or distribution capabilities. To achieve commercial success for Keyzilen®, Sonsuvi®, AM-125 and our other product candidates, we will have to develop our own sales, marketing and supply organization or outsource these activities to a third party.

Factors that may affect our ability to commercialize our product candidates on our own include recruiting and retaining adequate numbers of effective sales and marketing personnel, obtaining access to or persuading adequate numbers of physicians to prescribe our drug candidates and other unforeseen costs associated with creating an independent sales and marketing organization. Developing a sales and marketing organization requires significant investment, is time-consuming and could delay the launch of our product candidates. We may not be able to build an effective sales and marketing organization. If we are unable to build our own distribution and marketing capabilities or to find suitable partners for the commercialization of our product candidates, we may not generate revenues from them or be able to reach or sustain profitability.

Risks Related to Our Reliance on Third Parties

We have several areas of disagreement with Xigen, and consequently our relationship with Xigen may be adversely affected, we could potentially lose our right to commercialize Sonsuvi® and our business, commercialization prospects and financial condition may be adversely affected.

We have several areas of disagreement with Xigen S.A., or Xigen, with whom we have an agreement pursuant to which Xigen granted us an exclusive worldwide license to use specified compounds to develop, manufacture and commercialize "pharmaceutical products as well as drug delivery devices and formulations for local administration of therapeutic substances to the inner ear for the treatment of ear disorders" (the Area). We differ from Xigen in our interpretation of the definition of the Area. We interpret "Area," as it pertains to pharmaceutical products, as not limited to local administration to the inner ear, but inclusive of the use of pharmaceutical products generally for the treatment of ear disorders (and that the limitation of "local administration to the inner ear" applies only to "drug delivery devices and formulations"). Xigen has adopted the interpretation that the license is limited to local administration for both pharmaceutical products and drug delivery and formulations. This difference in interpretation has no impact on our current or planned use of Sonsuvi® delivered locally via intratympanic treatment.

In addition, in October 2013, Xigen assigned certain of the patents relevant to the agreement to Xigen Inflammation Ltd., an unaffiliated entity organized in Cyprus. We consider this transfer to be in breach of the agreement since our prior written approval was not sought, although Xigen Inflammation Ltd. has confirmed to us that the assignment of patents is without prejudice to our license for local administration. In the past, Xigen has also requested from us quantities of Sonsuvi® for certain analyses, although we believe the quantities requested exceed what laboratories would generally require for such tests.

The agreement contains a confidentiality provision restricting the disclosure of the terms of the agreement. We believe that Xigen may have waived the confidentiality provision of the agreement by disclosing the terms of the agreement to Xigen Inflammation Ltd., although Xigen has denied that any disclosure of the agreement has been made to the assignee despite the assignee's assurance that the assignment was without prejudice to our license for local administration. Despite this, in connection with our initial public offering, we sought Xigen's consent to disclose certain provisions of the agreement and file a redacted version of the agreement with the SEC. Xigen, however, was only willing to provide its consent if we agreed to limit the scope of the definition of "Area," desist from claims that the transfer of patents to Xigen Inflammation Ltd. was in breach of the agreement and provide Xigen with certain quantities of the active substance of Sonsuvi® for analysis.

We believe Xigen's demands were unreasonable and unwarranted, and therefore we were not able to come to an agreement with Xigen prior to disclosing certain provisions of the agreement in the prospectus relating to our initial public offering and filing a redacted version of the agreement. Xigen may consider such disclosure to be a breach of the confidentiality provision of the agreement. The agreement is governed by Swiss law, and the venue is Solothurn, Switzerland. In the opinion of our Swiss counsel, while there can be no assurances, this disclosure by us does not rise to the level of material breach that would allow Xigen to repudiate the agreement.

We cannot predict the result of these disagreements with Xigen and any litigation that may result. While Xigen has taken no action as of the date of this Annual Report, Xigen may attempt to repudiate the contract and initiate a claim for damages against us. According to our Swiss counsel, Xigen would have to show that it had suffered a loss due to the disclosure of the redacted agreement and certain provisions of the agreement in the prospectus associated with our initial public offering, and the damages could be equal to the amount of the effective direct damage that Xigen proves it has suffered.

These disagreements, and in particular any resulting litigation, could result in substantial legal expenses, distraction to our management and employees and potentially the loss of our right to commercialize Sonsuvi®. No assurance can be given that these disagreements and any resulting litigation will not have a material adverse effect on our business, commercialization prospects for Sonsuvi® and our other product candidates and our financial condition. For a description of our agreement with Xigen. See "Business — Business overview — Collaboration and License Agreements — Xigen."

If we fail to maintain our current strategic relationships with INSERM and Xigen, our business, commercialization prospects and financial condition may be materially adversely affected.

We have a co-ownership/exploitation agreement with the *Institut National de la Santé et de la Recherche Médicale*, or INSERM, governing the exploitation of any products derived from patents that resulted from our joint research program with INSERM that was conducted in 2003 to 2005. Under this agreement with INSERM, we are given the exclusive right to exploit the patents issuing from the filed patent applications for all claimed applications, including the treatment of tinnitus, in order to develop, promote, manufacture, cause to be manufactured, use, sell and distribute any products, processes or services deriving from such patents, including Keyzilen®, in any country in which these patent applications have been filed during the term of the agreement. We alone are entitled to grant manufacturing or sales licenses for any patents to our subsidiaries and/or third parties. INSERM is entitled to use the inventions covered by the patents and applications for its own research purposes, free of charge, but may not generate any direct or indirect profits from such use. We have agreed to finance any additional research and development work necessary to obtain marketing authorizations for inventions covered by these patents and applications. If we fail to use reasonable efforts in carrying out this additional research, then INSERM may revoke the exclusivity of exploitation granted to us under this agreement. Additionally, we have an exclusive worldwide license from Xigen for the application of Xigen's novel intracellular peptide therapeutics in the area of ear disorders. These intellectual property rights have been the basis of our research and development of Keyzilen® and Sonsuvi®.

Good relationships with INSERM and Xigen are important for our business prospects. If our relationships with INSERM or Xigen were to deteriorate substantially or INSERM or Xigen were to challenge our use of their intellectual property or our calculations of the payments we owe under our agreements, our business, financial condition, commercialization prospects and results of operations could be materially adversely affected.

We may seek to form additional strategic alliances in the future with respect to our product candidates, and if we do not realize the benefits of such alliance, our business, financial condition, commercialization prospects and results of operations may be materially adversely affected.

Our product development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses and may require expertise, such as sales and marketing expertise, which we do not currently possess. Therefore, in addition to our relationships with INSERM and Xigen, for our Keyzilen® and Sonsuvi® product candidates respectively, for one or more of our product candidates, we may decide to enter into strategic alliances, or create joint ventures or collaborations with pharmaceutical or biopharmaceutical companies for the further development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Collaborations are complex and time-consuming to negotiate and document. Any delays in entering into new strategic partnership agreements related to our product candidates could delay the development and commercialization of our product candidates and reduce their competitiveness even if they reach the market. We may also be restricted under existing and future collaboration agreements from entering into strategic partnerships or collaboration agreements on certain terms with other potential collaborators. We may not be able to negotiate collaborations on acceptable terms, or at all, for any of our existing or future product candidates and programs because the potential partner may consider that our research and development pipeline is insufficiently developed to justify a collaborative effort, or that our product candidates and programs do not have the requisite potential to demonstrate safety and efficacy in the target population. If we are unsuccessful in establishing and maintaining a collaboration with respect to a particular product candidate, we may have to curtail the development of that product candidate, reduce the scope of or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of our sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense for which we have not budgeted. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we will not be able to bring our product candidates to market and generate product revenue. Even if we are successful in establishing a new strategic partnership or entering into a collaboration agreement, we cannot be certain that, following such a strategic transaction or license, we will be able to progress the development and commercialization of the applicable product candidates as envisaged, or that we will achieve the revenues that would justify such transaction, and we could be subject to the following risks, each of which may materially harm our business, commercialization prospects and financial condition:

- we may not be able to control the amount and timing of resources that the collaboration partner devotes to the product development program;
- the collaboration partner may experience financial difficulties;
- we may be required to relinquish important rights such as marketing, distribution and intellectual property rights;
- a collaboration partner could move forward with a competing product developed either independently or in collaboration with third parties, including our competitors; or
- business combinations or significant changes in a collaboration partner's business strategy may adversely affect our willingness to complete our obligations under any arrangement.

We rely on third parties to conduct our nonclinical and clinical trials and perform other tasks for us. If these third parties do not successfully carry out their contractual duties, meet expected deadlines, or comply with regulatory requirements, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.

We have relied upon and plan to continue to rely upon third-party CROs to monitor and manage data for our ongoing nonclinical and clinical programs, including the clinical trials of Keyzilen®, Sonsuvi®, AM-125 and AM-201. We rely on these parties for execution of our nonclinical and clinical studies and control only certain aspects of their activities. Nevertheless, we are responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards and our reliance on the CROs does not relieve us of our regulatory responsibilities. We and our CROs and other vendors are required to comply with cGMP, cGCP, and Good Laboratory Practice, or GLP, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Union and comparable foreign regulatory authorities for all of our product candidates in nonclinical and clinical development. Regulatory authorities enforce these regulations through periodic inspections of study sponsors, principal investigators, trial sites and other contractors. If we or any of our CROs or vendors fail to comply with applicable regulations, the data generated in our nonclinical and clinical trials may be deemed unreliable and the EMA, FDA, other regulatory authorities may require us to perform additional nonclinical and clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that all of our clinical trials comply with cGCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

If any of our relationships with these third-party CROs terminates, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our on-going nonclinical and clinical programs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our protocols, regulatory requirements, or for other reasons, our clinical trials may be extended, delayed, or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. CROs may also generate higher costs than anticipated. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenue could be delayed.

Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition, and prospects.

We currently rely on third-party suppliers and other third parties for production of our product candidates and our dependence on these third parties may impair the advancement of our research and development programs and the development of our product candidates.

We currently rely on and expect to continue to rely on third parties, for the manufacturing and supply of chemical compounds for the clinical trials of our product candidates, including Keyzilen®, Sonsuvi®, AM-125 and AM-201, and others for the manufacturing and supply of pre-filled syringes and spray pumps. For the foreseeable future, we expect to continue to rely on such third parties for the manufacture of any of our product candidates on a clinical or commercial scale, if any of our product candidates receives regulatory approval. Reliance on third-party providers may expose us to different risks than if we were to manufacture product candidates ourselves. The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA or other regulatory authorities pursuant to inspections that will be conducted after we submit our NDA or comparable marketing application to the FDA or other regulatory authority. Although we have auditing rights with all our manufacturing counterparties, we do not have control over a supplier's or manufacturer's compliance with

these laws, regulations and applicable cGMP standards and other laws and regulations, such as those related to environmental health and safety matters. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. Any failure to achieve and maintain compliance with these laws, regulations and standards could subject us to the risk that we may have to suspend the manufacturing of our product candidates or that obtained approvals could be revoked, which would adversely affect our business and reputation. Furthermore, third-party providers may breach agreements they have with us because of factors beyond our control. They may also terminate or refuse to renew their agreements because of their own financial difficulties or business priorities, potentially at a time that is costly or otherwise inconvenient for us. If we were unable to find adequate replacement or another acceptable solution in time, our clinical trials could be delayed or our commercial activities could be harmed.

In addition, the fact that we are dependent on our suppliers and other third parties for the manufacture, storage and distribution of our product candidates means that we are subject to the risk that our product candidates and, if approved, commercial products may have manufacturing defects that we have limited ability to prevent or control. The sale of products containing such defects could result in recalls or regulatory enforcement action that could adversely affect our business, financial condition and results of operations.

Growth in the costs and expenses of components or raw materials may also adversely influence our business, financial condition and results of operations. Supply sources could be interrupted from time to time and, if interrupted, that supplies could be resumed (whether in part or in whole) within a reasonable time frame and at an acceptable cost or at all.

Our current and anticipated future dependence upon others for the manufacturing of Keyzilen®, Sonsuvi®, AM-125 and any other product candidate that we develop may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

The drug substance and drug product for our product candidates are currently acquired from single-source suppliers. The loss of these suppliers, or their failure to supply us with the drug substance or drug product, could materially and adversely affect our business.

We do not currently, and do not expect to in the future, independently conduct manufacturing activities for our product candidates, including Keyzilen®, Sonsuvi®, AM-125 and AM-201. We currently have a relationship with one supplier each, for the supply of the API of Keyzilen®, Sonsuvi®, AM-125 and AM-201. We are reliant upon single source third-party contract manufacturing organizations to manufacture and supply the drug substance and drug product and components thereof for each of Keyzilen®, Sonsuvi®, AM-125 and AM-201. We do not currently have any other suppliers for the drug substance or drug product of our product candidates and, although we believe that there are alternate sources of supply that could satisfy our clinical and commercial requirements, and we have performed some preliminary investigations to assess this availability, we cannot assure you that identifying alternate sources and establishing relationships with such sources would not result in significant delay in the development of our product candidates. Additionally, we may not be able to enter into supply arrangements with alternative suppliers on commercially reasonable terms, or at all. A delay in the development of our product candidates or having to enter into a new agreement with a different third party on less favorable terms than we have with our current suppliers could have a material adverse impact upon on our business.

Risks Related to Intellectual Property

If we or our licensors are unable to obtain and maintain effective patent rights for our technologies, product candidates or any future product candidates, or if the scope of the patent rights obtained is not sufficiently broad, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection, and confidentiality agreements to protect the intellectual property related to our technologies and product candidates. Our success depends in large part on our and our licensors' ability to obtain and maintain patent and other intellectual property protection in the United States and in other countries with respect to our proprietary technology and products.

We have sought to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and products that are important to our business. This process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost, in a timely manner or in all jurisdictions. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, in some circumstances, we do not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal and factual questions for which legal principles remain unsolved. The patent applications that we own or in-license may fail to result in issued patents with claims that cover our product candidates in the United States or in other foreign countries. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions remain confidential for a period of time after filing, and some remain so until issued. We cannot be certain that we were the first to file any patent application related to our product candidates, or whether we were the first to make the inventions claimed in our owned patents or pending patent applications, nor can we know whether those from whom we license patents were the first to make the inventions claimed or were the first to file. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. There is no assurance that all potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. 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, found unenforceable or invalidated, which could allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third party patent rights. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates, prevent others from designing around our claims or provide us with a competitive advantage. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

We, independently or together with our licensors, have filed several patent applications covering various aspects of our product candidates. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patent or whether any issued patents will be found invalid and unenforceable or will be challenged by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us after patent issuance could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced.

We may not have sufficient patent terms to effectively protect our products and business.

Patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Although various extensions may be available, the life of a patent, and the protection it affords, is limited. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours or otherwise provide us with a competitive advantage. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications.

While patent term extensions under the Hatch-Waxman Act in the United States and under supplementary protection certificates in Europe may be available to extend the patent exclusivity term for Keyzilen®, Sonsuvi®, AM-125 and AM-201, we cannot provide any assurances that any such patent term extension will be obtained and, if so, for how long. In addition, upon issuance in the United States any patent term can be adjusted based on certain delays caused by the applicant(s) or the U.S. Patent and Trademark Office, or USPTO. For example, a patent term can be reduced based on certain delays caused by the patent applicant during patent prosecution.

While in the United States there is a possibility of obtaining market protection independent from any patent protection for up to 3 and 5 years from approval, and in the European Union one may obtain data exclusivity of eight years from approval with an additional two years of market exclusivity (which can potentially be extended by one year), there is no assurance that we can obtain such data exclusivity and market protection with respect to Keyzilen®, Sonsuvi®, AM-125, or any of our other product candidates. Our issued patents and pending patent applications are expected to expire for Keyzilen® between 2025 and 2028, for Sonsuvi® between 2020 and 2027, and for AM-125 and AM-201 between 2025 and 2037, prior to any patent term extensions to which we may be entitled under applicable laws.

Patent policy and rule changes could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Assuming the other requirements for patentability are met, in the United States prior to March 15, 2013, the first to make the claimed invention is entitled to the patent, while outside the United States, the first to file a patent application is entitled to the patent. After March 15, 2013, under the Leahy-Smith America Invents Act, or the Leahy-Smith Act, enacted on September 16, 2011, the United States has moved to a first to file system. The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications will be prosecuted and may also affect patent litigation. The effects of these changes are currently unclear as the USPTO must still implement various regulations, the courts have yet to address any of these provisions and the applicability of the act and new regulations on specific patents discussed herein have not been determined and would need to be reviewed. In general, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition. In addition, recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

If we are unable to maintain effective proprietary rights for our technologies, product candidates or any future product candidates, we may not be able to compete effectively in our markets.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. Moreover, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such competitor from using that technology or information to compete with us, which could harm our competitive position.

Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors, and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating such trade secrets. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the U.S. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the U.S. and abroad. If we are unable to prevent material disclosure of the intellectual property related to our technologies to third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, financial condition and results of operations.

Third-party claims of intellectual property infringement may expose us to substantial liability or prevent or delay our development and commercialization efforts.

Our commercial success depends in part on our ability to develop, manufacture, market and sell our product candidates and use our proprietary technology without alleged or actual infringement, misappropriation, or other violation of the patents and proprietary rights of third parties. There have been many lawsuits and other proceedings involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions, and reexamination proceedings before the USPTO and corresponding foreign patent offices. Numerous U.S.- and foreign-issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates. Some claimants may have substantially greater resources than we do and may be able to sustain the costs of complex intellectual property litigation to a greater degree and for longer periods of time than we could. In addition, patent holding companies that focus solely on extracting royalties and settlements by enforcing patent rights may target us. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture, or methods of treatment related to the use or manufacture of our product candidates. Although we generally conduct certain freedom to operate search and review with respect to our product candidates, we cannot guarantee that any of our search and review is complete and thorough, nor can we be sure that we have identified each and every patent and pending application in the United States and abroad that is relevant or necessary to the commercialization of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire or are finally determined to be invalid or unenforceable. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture, or methods of use, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires or is finally determined to be invalid or unenforceable. In either case, such a license may not be available on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

Additional competitors could enter the market with generic versions of our products, which may result in a material decline in sales of affected products.

Under the Hatch-Waxman Act, a pharmaceutical manufacturer may file an abbreviated new drug application, or ANDA, seeking approval of a generic copy of an approved innovator product. Under the Hatch-Waxman Act, a manufacturer may also submit an NDA under section 505(b)(2) that references the FDA's prior approval of the innovator product. A 505(b)(2) NDA product may be for a new or improved version of the original innovator product. Hatch-Waxman also provides for certain periods of regulatory exclusivity, which preclude FDA approval (or in some circumstances, FDA filing and reviewing) of an ANDA, or 505(b)(2) NDA. These include, subject to certain exceptions, the period during which an FDA-approved drug is subject to orphan drug exclusivity. In addition to the benefits of regulatory exclusivity, an innovator NDA holder may have patents claiming the active ingredient, product formulation or an approved use of the drug, which would be listed with the product in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," known as the "Orange Book." If there are patents listed in the Orange Book, a generic or 505(b)(2) applicant that seeks to market its product before expiration of the patents must include in the ANDA what is known as a "Paragraph IV certification," challenging the validity or enforceability of, or claiming non-infringement of, the listed patent or patents. Notice of the certification must be given to the innovator, too, and if within 45 days of receiving notice the innovator sues to protect its patents, approval of the ANDA is stayed for 30 months, or as lengthened or shortened by the court.

Accordingly, if Keyzilen®, Sonsuvi®, AM-125 and AM-201 are approved, competitors could file ANDAs for generic versions of Keyzilen®, Sonsuvi®, AM-125 and AM-201, or 505(b)(2) NDAs that reference Keyzilen®, AM-111 and AM-125, respectively. If there are patents listed for Keyzilen®, Sonsuvi®, AM-125 and AM-201 in the Orange Book, those ANDAs and 505(b)(2) NDAs would be required to include a certification as to each listed patent indicating whether the ANDA applicant does or does not

intend to challenge the patent. We cannot predict whether any patents issuing from our pending patent applications will be eligible for listing in the Orange Book, how any generic competitor would address such patents, whether we would sue on any such patents, or the outcome of any such suit.

We may not be successful in securing or maintaining proprietary patent protection for products and technologies we develop or license. Moreover, if any patents that are granted and listed in the Orange Book are successfully challenged by way of a Paragraph IV certification and subsequent litigation, the affected product could immediately face generic competition and its sales would likely decline rapidly and materially. Should sales decline, we may have to write off a portion or all of the intangible assets associated with the affected product and our results of operations and cash flows could be materially and adversely affected.

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

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

The patent protection and patent prosecution for some of our product candidates is dependent on third parties.

While we normally seek to obtain the right to control prosecution, maintenance and enforcement of the patents relating to our product candidates, there may be times when the filing and prosecution activities for patents relating to our product candidates are controlled by our licensors. This is the case under our agreement with Xigen, where Xigen is entirely responsible for the prosecution and maintenance of the licensed patents and patent applications directed to Sonsuvi®. Xigen has no obligation to provide us any information with respect to such prosecution and we will not have access to any patent prosecution or maintenance information that is not publicly available. Although we monitor Xigen's ongoing prosecution and maintenance of the licensed patents, if Xigen or any of our future licensing partners fail to prosecute, maintain and enforce such patents and patent applications in a manner consistent with the best interests of our business, including by payment of all applicable fees for patents covering Sonsuvi® or any of our product candidates, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, our ability to develop and commercialize those product candidates may be adversely affected and we may not be able to prevent competitors from making, using, and selling competing products. Specifically, Xigen is concurrently developing another indication for brimapitide (XG-102), the active substance of Sonsuvi®. This may cause a conflict of interest and adversely affect Xigen's ability to prosecute the patent portfolio licensed to us in the best interest of our business. In addition, even where we have the right to control patent prosecution of patents and patent applications we have licensed from third parties including with respect to the patents and applications licensed to us under our co-ownership and exploitation agreement with INSERM for Keyzilen®, we may still be adversely affected or prejudiced by actions or inactions of our licensors and their counsel that took place prior to the date upon which we assumed control over patent prosecution. We are required to consult and cooperate with INSERM regarding the prosecution, maintenance, and enforcement of, and in certain instances INSERM has the right to independently enforce, the relevant patents, which may place those patients at risk or hinder our ability to develop and commercialize those product candidates or protect our patent rights.

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

We are a party to a number of intellectual property license and co-ownership agreements that are important to our business and expect to enter into additional such agreements in the future. Our existing agreements impose, and we expect that future agreements will impose, various diligence, commercialization, milestone payment, royalty, and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, we may be required to make certain payments to the licensor, we may lose the exclusivity of our license, or the licensor may have the right to terminate the license, in which event we would not be able to develop or market products covered by the license. Moreover, if we fail to comply with our obligations under our co-ownership and exploitation agreement with INSERM for Keyzilen®, including certain commercialization requirements, or we are subject to a bankruptcy, INSERM may terminate the agreement and we may lose our rights to exclusively exploit and commercialize the applicable patents. In such event we would not be able to prevent INSERM from exploiting or licensing to the third parties the rights to exploit the applicable patents, which would have a material adverse effect on our ability to successfully commercialize the affected product candidates. Under our co-ownership agreement with INSERM we may be required to assign our rights in the relevant patents to INSERM if we choose not to or fail to continue to prosecute maintain or patents or patent applications in a given country or countries, in which event we would not be able to develop or market products covered by the applicable patents.

Licensing of intellectual property is of critical importance to our business and involves complex legal, business, and scientific issues. Disputes may arise regarding intellectual property subject to a licensing or co-ownership agreement, including:

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

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

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

We currently have rights to the intellectual property, through licenses from third parties and under patents that we own, to develop our product candidates. Because our programs may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license, maintain or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently and the rights to these formulations may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes, or other third-party intellectual property rights from third parties that we identify as necessary for our product candidates. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources, and greater clinical development and commercialization capabilities.

For example, we sometimes collaborate with U.S. and foreign academic institutions to accelerate our pre-clinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our applicable product candidate or program.

In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain a license to third-party intellectual property rights necessary for the development of a product candidate or program, we may have to abandon development of that product candidate or program and our business and financial condition could suffer.

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

Competitors may infringe our patents or the patents of our licensors. To counter such infringement, we may be required to file claims against those competitors, which can be expensive and time-consuming. If we or one of our licensing partners were to initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid, overbroad and/or unenforceable, or that we infringe the defendant's patents. In patent litigation in the United States, defendant counterclaims alleging invalidity, overbreadth and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. The outcome following legal assertions of invalidity and unenforceability is unpredictable. A court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop a third party from using the technology in question on the grounds that our patents do not cover that technology. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly, which could adversely affect us.

Interference proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms or at all. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our product candidates to market. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions, or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common shares.

On July 20, 2015, the USPTO declared Patent Interference No. 106,030 involving our issued U.S. patent No. 9,066,865 (the "'865 Patent") and Otonomy's U.S. patent application No. 13/848,636 (the "'636 Application"). The patent interference identified claims 1-9 in the '865 Patent as interfering with claims 38, 43 and 46-50 of the '636 Application. The '865 Patent discloses methods of treating inner or middle ear diseases with intratympanic injections of poloxamer-based compositions. The claims of the '865

Patent are directed to the use of fluoroquinolone antibiotics in poloxamer 407 compositions under certain specifications. On January 26, 2017, the USPTO issued a decision on the interference granting Auris benefit of priority. As a result of the decision, judgment was entered against Otonomy and all claims in the '636 Application were refused. In addition, claims 1-8 of the '865 Patent were cancelled as the result of the USPTO's determination that the written description of the specification lacked full scope support for treating middle or inner ear disease with fluoroquinolone. However, claim 9, which is directed to a method of treating viral and bacterial infections with intratympanic injection of a fluoroquinolone antibiotic in a poloxamer 407 composition under certain specifications, was affirmed. On March 27, 2017, Otonomy submitted a notice of appeal to the United States Court of Appeals for the Federal Circuit. To preserve its rights, Auris filed a notice of cross-appeal on April 5, 2017. Otonomy subsequently filed its opening brief on July 20, 2017, and Auris filed its principal and response brief on October 27, 2017. On January 5, 2018, Otonomy filed its opposition and reply brief. Auris filed its reply brief on February 2, 2018. On August 1, 2018, the United States Court of Appeals for the Federal Circuit reversed the USPTO Patent Trial and Appeal Board's determination of priority in our favor relating to the July 2015 USPTO declaration of patent interference (No. 106,030) involving our issued '865 Patent and Otonomy's '636 Application. We believe that this ruling will not materially impact any of our development programs.

We may be subject to claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ and utilize the services of individuals who were previously employed or provided services to universities or other biotechnology or pharmaceutical companies. Although we try to ensure that our employees, consultants, and independent contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees, consultants, or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any of our employee's, consultant's or independent contractor's former employer or other third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact 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 other employees.

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

Because we rely on our advisors, employees and third-party contractors and consultants to research and develop and to manufacture our product candidates, we must, at times, share our intellectual property with them. We seek to protect our intellectual property and other proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of these advisors, employees and third parties to use or disclose our confidential information, including our intellectual property and trade secrets. Despite the contractual provisions employed when working with these advisors, employees and third parties, the need to share intellectual property and other confidential information increases the risk that such confidential information becomes known by our competitors, are inadvertently incorporated into the product development of others or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how, intellectual property and trade secrets, a competitor's discovery of our intellectual property or trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our intellectual property, although our agreements may contain certain limited publication rights. For example, any academic institution that we may collaborate with in the future may expect to be granted rights to publish data arising out of such

collaboration, provided that we are notified in advance and given the opportunity to delay publication for a limited time period in order for us to secure patent protection of intellectual property rights arising from the collaboration, in addition to the opportunity to remove confidential or trade secret information from any such publication. In the future, we may also conduct joint research and development programs that may require us to share intellectual property under the terms of our research and development or similar agreements. Despite our efforts to protect our intellectual property, our competitors may discover our trade secrets or know how, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. A competitor's discovery of our intellectual property would impair our competitive position and have an adverse impact on our business.

We may be subject to claims challenging the inventorship of our patents and other intellectual property.

We may be subject to claims that former employees, collaborators or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. For example, we may have inventorship disputes arise from 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 our ownership of our patents or other intellectual property. If we 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 other employees.

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

Filing, prosecuting, and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. As part of ordinary course prosecution and maintenance activities, we determine whether to seek patent protection outside the U.S. and in which countries. This also applies to patents we have acquired or in-licensed from third parties. In some cases this means that we, or our predecessors in interest or licensors of patents within our portfolio, have sought patent protection in a limited number of countries for patents covering our product candidates. Competitors may use our technologies in jurisdictions where we have not obtained or are unable to adequately enforce patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents, the reproduction of our manufacturing or other know-how or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Risks Related to Employee Matters and Managing Growth

Our future growth and ability to compete depends on retaining our key personnel and recruiting additional qualified personnel.

Our success depends upon the continued contributions of our key management, scientific and technical personnel, many of whom have substantial experience with or been instrumental for us and our projects. Key management includes our executive officers Thomas Meyer, our founder, Chairman and Chief Executive Officer and Hernan Levett, Chief Financial Officer.

The loss of key managers and senior scientists could delay our research and development activities. Laws and regulations on executive compensation, including legislation in Switzerland, may restrict our ability to attract, motivate and retain the required level of qualified personnel. If the Redomestication is not approved, we will remain impacted by legislation in Switzerland affecting public companies that, among other things, (a) imposes an annual binding shareholders' "say on pay" vote with respect to the compensation of executive management, including executive officers and the board of directors, (b) prohibits severance, advances, transaction premiums and similar payments to executive officers and directors and (c) requires companies to specify various compensation-related matters in their articles of association, thus requiring them to be approved by a shareholders' vote. In addition, the competition for qualified personnel in the biopharmaceutical and pharmaceutical field is intense, and our future success depends upon our ability to attract, retain and motivate highly-skilled scientific, technical and managerial employees. We face competition for personnel from other companies, universities, public and private research institutions and other organizations. If our recruitment and retention efforts are unsuccessful in the future, it may be difficult for us to implement business strategy, which could have a material adverse effect on our business.

We expect to expand our sales and marketing, development, and regulatory capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of sales and marketing, and to a lesser extent, drug development and regulatory affairs. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks Related to Our Common Shares

The price of our common shares may be volatile and may fluctuate due to factors beyond our control.

The share price of publicly traded emerging biopharmaceutical and drug discovery and development companies has been highly volatile and is likely to remain highly volatile in the future. The market price of our common shares may fluctuate significantly due to a variety of factors, including:

- positive or negative results of testing and clinical trials by us, strategic partners, or competitors;
- delays in entering into strategic relationships with respect to development and/or commercialization of our product candidates or entry into strategic relationships on terms that are not deemed to be favorable to us;
- technological innovations or commercial product introductions by us or competitors;
- changes in government regulations;
- developments concerning proprietary rights, including patents and litigation matters;
- public concern relating to the commercial value or safety of any of our product candidates;

- financing or other corporate transactions;
- publication of research reports or comments by securities or industry analysts;
- general market conditions in the pharmaceutical industry or in the economy as a whole; or
- other events and factors beyond our control.

Additionally, these factors may affect the liquidity of our common shares, which may hurt your ability to sell our common shares in the future. In addition, the stock market in general has recently experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of individual companies. Broad market and industry factors may materially affect the market price of companies' stock, including ours, regardless of actual operating performance.

Our common shares may be involuntarily delisted from trading on The Nasdaq Capital Market if we fail to comply with the continued listing requirements. A delisting of our common shares is likely to reduce the liquidity of our common shares and may inhibit or preclude our ability to raise additional financing.

We are required to comply with certain Nasdaq continued listing requirements, including a series of financial tests relating to shareholder equity, market value of listed securities and number of market makers and shareholders. If we fail to maintain compliance with any of those requirements, our common shares could be delisted from The Nasdaq Capital Market.

We are currently not in compliance with the quantitative listing standards of the Nasdaq Capital Market, which require, among other things, that listed companies maintain a minimum closing bid price of $1.00 per share. We failed to satisfy this threshold for 30 consecutive trading days and on July 30, 2018, we received a letter from Nasdaq indicating that we have been provided a period of 180 calendar days in which to regain compliance. We are in contact with Nasdaq regarding a plan to regain compliance. In the event that Nasdaq does not grant us an additional compliance period or we fail to regain compliance by the end of such additional compliance period, our board of directors will weigh the available alternatives to regain compliance, including pursuing a reverse share split by consolidating our common shares (together with a corresponding increase in the par value thereof) in a ratio determined by the board of directors. In the event shareholders approve the Bye-laws, Auris Medical (Bermuda)'s board of directors could, after the Redomestication, effect a reverse share split without further shareholders approval, by consolidating our common shares (together with a corresponding increase in the par value thereof) in a ratio determined by the board of directors. However, there can be no assurance that we will be able to successfully resolve such noncompliance.

In 2017, we also failed to maintain compliance with the minimum bid price requirement. To address that non-compliance, on March 13, 2018, we effected the Merger, pursuant to which we effected a "reverse share split" at a ratio of 10-for-1. Additionally, on January 11, 2018, we received a letter from Nasdaq indicating that we were not in compliance with Nasdaq's market value of listed securities requirement. As a result of the July 2018 Registered Offering, we resolved the non-compliance with the market value of listed securities requirement by complying with Nasdaq's minimum equity standard. However, there can be no assurance that we will be able to successfully maintain compliance with the several Nasdaq continued listing requirements.

If, for any reason, Nasdaq should delist our common shares from trading on its exchange and we are unable to obtain listing on another national securities exchange or take action to restore our compliance with the Nasdaq continued listing requirements, a reduction in some or all of the following may occur, each of which could have a material adverse effect on our shareholders:

- the liquidity of our common shares;
- the market price of our common shares;
- our ability to obtain financing for the continuation of our operations;
- the number of institutional and general investors that will consider investing in our common shares;
- the number of investors in general that will consider investing in our common shares;

- the number of market makers in our common shares;
- the availability of information concerning the trading prices and volume of our common shares; and
- the number of broker-dealers willing to execute trades in shares of our common shares.

In the event that our common shares are delisted from Nasdaq, U.S. broker-dealers may be discouraged from effecting transactions in shares of our common shares because they may be considered penny stocks and thus be subject to the penny stock rules.

The SEC has adopted a number of rules to regulate "penny stock" that restrict transactions involving stock which is deemed to be penny stock. Such rules include Rules 3a51-1, 15g-1, 15g-2, 15g-3, 15g-4, 15g-5, 15g-6, 15g-7, and 15g-9 under the Exchange Act. These rules may have the effect of reducing the liquidity of penny stocks. "Penny stocks" generally are equity securities with a price of less than $5.00 per share (other than securities registered on certain national securities exchanges or quoted on the Nasdaq Stock Market if current price and volume information with respect to transactions in such securities is provided by the exchange or system). Our common shares have in the past constituted, and may again in the future constitute, "penny stock" within the meaning of the rules. The additional sales practice and disclosure requirements imposed upon U.S. broker-dealers may discourage such broker-dealers from effecting transactions in shares of our common shares, which could severely limit the market liquidity of such common shares and impede their sale in the secondary market.

A U.S. broker-dealer selling penny stock to anyone other than an established customer or "accredited investor" (generally, an individual with net worth in excess of $1,000,000 or an annual income exceeding $200,000, or $300,000 together with his or her spouse) must make a special suitability determination for the purchaser and must receive the purchaser's written consent to the transaction prior to sale, unless the broker-dealer or the transaction is otherwise exempt. In addition, the "penny stock" regulations require the U.S. broker-dealer to deliver, prior to any transaction involving a "penny stock", a disclosure schedule prepared in accordance with SEC standards relating to the "penny stock" market, unless the broker-dealer or the transaction is otherwise exempt. A U.S. broker-dealer is also required to disclose commissions payable to the U.S. broker-dealer and the registered representative and current quotations for the securities. Finally, a U.S. broker-dealer is required to submit monthly statements disclosing recent price information with respect to the "penny stock" held in a customer's account and information with respect to the limited market in "penny stocks."

Shareholders should be aware that, according to the SEC, the market for "penny stocks" has suffered in recent years from patterns of fraud and abuse. Such patterns include (i) control of the market for the security by one or a few broker-dealers that are often related to the promoter or issuer; (ii) manipulation of prices through prearranged matching of purchases and sales and false and misleading press releases; (iii) "boiler room" practices involving high-pressure sales tactics and unrealistic price projections by inexperienced sales persons; (iv) excessive and undisclosed bid-ask differentials and markups by selling broker-dealers; and (v) the wholesale dumping of the same securities by promoters and broker-dealers after prices have been manipulated to a desired level, resulting in investor losses. Our management is aware of the abuses that have occurred historically in the penny stock market. Although we do not expect to be in a position to dictate the behavior of the market or of broker-dealers who participate in the market, management will strive within the confines of practical limitations to prevent the described patterns from being established with respect to our securities.

Certain principal shareholders and members of our executive team and board of directors own a majority of our common shares and as a result will be able to exercise significant control over us, and your interests may conflict with the interests of such shareholders.

Certain principal shareholders and their affiliated entities as well as members of our executive team and board of directors own approximately 17% of our common shares. Depending on the level of attendance at our general meetings of shareholders, these shareholders may be in a position to determine the outcome of decisions taken at any such general meeting. Any shareholder or group of shareholders controlling more than 50% of the shares represented at our general meetings of shareholders may control

any shareholder resolution requiring an absolute majority of the shares represented, including the election of members to the board of directors of the Company, certain decisions relating to our capital structure, the approval of certain significant corporate transactions and certain amendments to our articles of association. To the extent that the interests of these shareholders may differ from the interests of the Company's other shareholders, the latter may be disadvantaged by any action that these shareholders may seek to pursue. Among other consequences, this concentration of ownership may have the effect of delaying or preventing a change in control and might therefore negatively affect the market price of our common shares.

Future sales, or the possibility of future sales, of a substantial number of our common shares could adversely affect the price of our common shares.

Future sales of a substantial number of our common shares, or the perception that such sales will occur, could cause a decline in the market price of our common shares. Approximately 17% of our common shares outstanding are held by affiliates. If these shareholders sell substantial amounts of common shares in the public market, or the market perceives that such sales may occur, the market price of our common shares and our ability to raise capital through an issue of equity securities could be adversely affected. Additionally, as of the date of this proxy statement/prospectus we have warrants outstanding, which are exercisable for an aggregate of 6,544,791 common shares at a weighted average exercise price of $2.33 per share, an equity commitment to sell up to $9.0 million of additional common shares to Lincoln Park Capital Fund, LLC ("LPC") pursuant to the commitment purchase agreement we entered into on May 2, 2018 with LPC (the "LPC Purchase Agreement") and an at-the-market offering program pursuant to the sales agreement we entered into with A.G.P./Alliance Global Partners ("A.G.P.") on November 30, 2018 (the "A.G.P. Sales Agreement") for sales of up to $25.0 million of additional common shares. In connection with the Redomestication, we will be unable to raise capital through the LPC Purchase Agreement or the A.G.P. Sales Agreement unless we successfully renegotiate such agreements with the relevant counter-parties. We cannot be certain that we will be able to negotiate such agreements with the same terms and conditions, or at all. We have also entered into a registration rights agreement pursuant to which we have agreed under certain circumstances to file a registration statement to register the resale of common shares held by certain of our shareholders, as well as to cooperate in certain public offerings of such common shares. We have also filed registration statements to register the resale of the common shares underlying the warrants that we have offered and sold in unregistered transactions, the common shares that are sold to LPC and the common shares and other equity securities that we have issued under our prior equity incentive plans or may issue under our new omnibus equity compensation plan. These common shares may be freely sold in the public market upon issuance, subject to certain limitations applicable to affiliates. In addition, we have filed a registration statement covering the issuance and sale by us of up to $100 million of common shares, debt securities, warrants, purchase contracts, units and common shares. We may issue such securities, including our common shares and warrants to purchase common shares, at any time and from time to time subject to the limitations set forth in General Instruction I.B.5 of Form F-3. If a large number of our common shares and/or warrants to purchase common shares are sold in the public market, the sales could reduce the trading price of our common shares and impede our ability to raise future capital.

We do not expect to pay dividends in the foreseeable future.

We have not paid any dividends since our incorporation. Even if future operations lead to significant levels of distributable profits, we currently intend that any earnings will be reinvested in our business and that dividends will not be paid until we have an established revenue stream to support continuing dividends. Following the Redomestication, the proposal to pay future dividends to shareholders will in addition effectively be at the discretion of our board of directors after taking into account various factors including our business prospects, cash requirements, financial performance and new product development. In addition, payment of future dividends is subject to certain limitations pursuant to Swiss law or by our articles of association. If the Redomestication is effected, we will be subject to Bermuda law restrictions on the payment of dividends including that no dividends may be declared by our board of directors or paid by the Company if there are reasonable grounds for believing that: (i) we are, or would after the payment be, unable to pay our liabilities as they become due; or (ii) that the realizable value of our assets would thereby be less than our liabilities. Accordingly, investors cannot rely on dividend income from our common shares and any returns on an investment in our common shares will likely depend entirely upon any future appreciation in the price of our common shares.

Additionally, in connection with the Merger, the Swiss Federal Tax Administration took the position (on the basis of a tax ruling) that, as a result of the Merger, the existing Capital Contribution Reserves will be offset against the retained losses. This leads to a reduced amount of Capital Contribution Reserves. We do not intend to make distributions in the foreseeable future, but if the position of the tax authorities were to prevail, it is likely that any distributions exceeding the reduced amount of Capital Contributions Reserves would be treated as taxable dividends for Swiss tax purposes. If we ever decide to declare dividends, we expect to challenge the view under the tax ruling, but there can be no assurance that any such challenge would be successful.

We are a holding company with no material direct operations.

We are a holding company with no material direct operations. As a result, we would be dependent on dividends, other payments or loans from our subsidiaries in order to pay a dividend. Our subsidiaries are subject to legal requirements of their respective jurisdictions of organization that may restrict their paying dividends or other payments, or making loans, to us.

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

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

As a foreign private issuer and as permitted by the listing requirements of Nasdaq, we follow certain home country governance practices rather than the corporate governance requirements of Nasdaq.

We are a foreign private issuer. As a result, in accordance with Nasdaq Listing Rule 5615(a)(3), we comply with home country governance requirements and certain exemptions thereunder rather than complying with certain of the corporate governance requirements of Nasdaq.

Neither Swiss law nor Bermuda law requires that a majority of our board of directors consists of independent directors. Our board of directors therefore may include fewer independent directors than would be required if we were subject to Nasdaq Listing Rule 5605(b)(1). In addition, we are not subject to Nasdaq Listing Rule 5605(b)(2), which requires that independent directors regularly have scheduled meetings at which only independent directors are present.

Although Swiss law also requires that we adopt a compensation committee, we follow home country requirements with respect to such committee. As a result, our practice varies from the requirements of Nasdaq Listing Rule 5605(d), which sets forth certain requirements as to the responsibilities, composition and independence of compensation committees. We follow Swiss law requirements with respect to disclosure of compensation for our directors and executive officers. Neither Swiss law nor Bermuda law requires that we disclose information regarding third-party compensation of our directors or director nominee. As a result, our practice varies from the third-party compensation disclosure requirements of Nasdaq Listing Rule 5250(b)(3). After the Redomestication, we intend to follow the requirements of

Bermuda law with respect to our compensation committee, disclosure of compensation of our directors and executive officers and information regarding third-party compensation of our directors or director nominee, each of which differ from the requirements of the Nasdaq Listing Rules.

In addition, as permitted by with Swiss law and Bermuda law, we have opted not to implement a standalone nominating committee. To this extent, our practice varies from the independent director oversight of director nominations requirements of Nasdaq Listing Rule 5605(e).

Furthermore, in accordance with Swiss law and generally accepted business practices, our constitutive documents do not provide quorum requirements generally applicable to general meetings of shareholders. After the Redomestication, the quorum for a general meeting of shareholders will be as set out in the Bye-laws, which will provide for a quorum of two or more persons present at the start of the meeting and representing in person or by proxy issued and outstanding voting shares in the company. Our practice thus varies from the requirement of Nasdaq Listing Rule 5620(c), which requires an issuer to provide in its bylaws for a generally applicable quorum, and that such quorum may not be less than one-third of the outstanding voting stock. Our constitutive documents provide for an independent proxy holder elected by our shareholders, who may represent our shareholders at a general meeting of shareholders, and we must provide shareholders with an agenda and other relevant documents for the general meeting of shareholders. However, neither Swiss law nor Bermuda law has a regulatory regime for the solicitation of proxies, thus our practice varies from the requirement of Nasdaq Listing Rule 5620(b), which sets forth certain requirements regarding the solicitation of proxies. In addition, we have opted out of shareholder approval requirements for the issuance of securities in connection with certain events such as the acquisition of stock or assets of another company, the establishment of or amendments to equity-based compensation plans for employees, a change of control of us and certain private placements. To this extent, our practice varies from the requirements of Nasdaq Listing Rule 5635, which generally requires an issuer to obtain shareholder approval for the issuance of securities in connection with such events.

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

We may lose our foreign private issuer status, which would then require us to comply with the Exchange Act's domestic reporting regime and cause us to incur significant legal, accounting and other expenses.

We are a foreign private issuer and therefore we are not required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers. In order to maintain our current status as a foreign private issuer, either (a) a majority of our common shares must be either directly or indirectly owned of record by non-residents of the United States or (b)(i) a majority of our executive officers or directors may not be United States citizens or residents, (ii) more than 50 percent of our assets cannot be located in the United States and (iii) our business must be administered principally outside the United States. These criteria are tested on the last business day of our second fiscal quarter, each year. If we lost this status, we would be required to comply with the Exchange Act reporting and other requirements applicable to U.S. domestic issuers, which are more detailed and extensive than the requirements for foreign private issuers. We may also be required to make changes in our corporate governance practices in accordance with various SEC and stock exchange rules. The regulatory and compliance costs to us under U.S. securities laws if we are required to comply with the reporting requirements applicable to a U.S. domestic issuer may be significantly higher than the cost we would incur as a foreign private issuer. As a result, we expect that a loss of foreign private issuer status would increase our legal and financial compliance costs and would make some activities highly time-consuming and costly. We also expect that if we were required to comply with the rules and regulations applicable to U.S. domestic issuers, it would make it more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our board of directors.

We are an "emerging growth company," and we cannot be certain if the reduced reporting requirements applicable to "emerging growth companies" will make our common shares less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act. For as long as we continue to be an "emerging growth company," we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not "emerging growth companies," including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We could be an "emerging growth company" until 2019, although circumstances could cause us to lose that status earlier, including if the market value of our common shares held by non-affiliates exceeds $700 million as of any June 30 (the end of our second fiscal quarter) before that time, in which case we would no longer be an "emerging growth company" as of the following December 31 (our fiscal year end). We cannot predict if investors will find our common shares less attractive because we may rely on these exemptions. If some investors find our common shares less attractive as a result, there may be a less active trading market for our common shares and the price of our common shares may be more volatile.

We believe that we were a "passive foreign investment company," or PFIC, for U.S. federal income tax purposes for our 2018 taxable year, and we expect to be a PFIC for our current year and for the foreseeable future.

We believe that we were a "passive foreign investment company," or PFIC, for U.S. federal income tax purposes for our 2018 taxable year, and we expect to be a PFIC for our current year and for the foreseeable future. In addition, we may, directly or indirectly, hold equity interests in other PFICs. Under the Internal Revenue Code of 1986, as amended, we will be a PFIC for any taxable year in which (i) 75% or more of our gross income consists of passive income or (ii) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as if it held its proportionate share of the assets of the other corporation and received directly its proportionate share of the income of the other corporation. Passive income generally includes dividends, interest, rents, royalties and capital gains.

If we are a PFIC for any taxable year during which a U.S. investor holds our shares, the U.S. investor may be subject to adverse tax consequences, including (i) the treatment of all or a portion of any gain on disposition as ordinary income, (ii) the application of a deferred interest charge on such gain and the receipt of certain dividends and (iii) compliance with certain reporting requirements.

For further discussion of the adverse U.S. federal income tax consequences of our classification as a PFIC, see "Material U.S. Federal Income Tax Considerations for U.S. Holders."

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our common shares.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404 of the Sarbanes-Oxley Act of 2002, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also subject us to regulatory scrutiny and sanctions, impair our ability to raise revenue and cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our common shares.

We will be required to disclose changes made in our internal controls and procedures and our management will be required to assess the effectiveness of these controls annually. However, for as long as we are an "emerging growth company" under the JOBS Act, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. We could be an "emerging growth company" until August 2019. An independent assessment of the effectiveness of our internal controls could detect problems that our management's assessment might not. Undetected material weaknesses in our internal controls could lead to financial statement restatements and require us to incur the expense of remediation.

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

The trading market for our common shares depends in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. We cannot assure you that analysts will cover us or provide favorable coverage. If one or more of the analysts who cover us downgrade our common shares or publish inaccurate or unfavorable research about our business, the price of our common shares would likely decline. If one or more of these analysts cease coverage of the Company or fail to publish reports on us regularly, demand for our common shares could decrease, which might cause the price of our common shares and trading volume to decline.

Risks Related to the Change in Our Jurisdiction of Incorporation

Currently, your rights as a shareholder of Auris Medical Holding AG arise under Swiss law as well as our existing Swiss articles of association. Upon Redomestication, your rights as a shareholder of Auris Medical (Bermuda) will arise under Bermuda law, the Memorandum of Continuance and the Bye-laws to be adopted in accordance with Bermuda law.

The Memorandum of Continuance and the Bye-laws of Auris Medical (Bermuda) will be the constitutive documents of Auris Medical (Bermuda) upon Redomestication, assuming shareholder approval of the Redomestication, the Memorandum of Continuance and the Bye-laws. These new constitutive documents and Bermuda law will contain provisions that differ from those in our current constitutive documents and Swiss law and, therefore, your rights as a shareholder of Auris Medical (Bermuda) could differ materially from the rights you currently possess as a shareholder of Auris Medical Holding AG. For instance, upon effectiveness of the Redomestication, the Swiss OaEC (*VegüV*) will no longer apply to the Company. The OaEC contains numerous provisions that serve to increase the transparency and provide shareholders with a right to voice their opinions on compensation matters. Pursuant to the OaEC, Swiss companies are, among others, obliged to have a framework in place according to which (i) the shareholders each year elect the members of the board of directors separately, (ii) the shareholders each year elect the chairman of the board of directors, (iii) the shareholders each year elect the members of the compensation committee and the independent proxy and (iv) the shareholders each year separately approve the compensation of the members of the board of directors, the management and the advisory board. The OaEC further contains provisions according to which the board of directors for each year has to prepare a written compensation report which has to be approved by the shareholders, detailing the compensations paid to each member of the board of directors, the management and the advisory board. In addition, companies that are subject to the OaEC are generally not allowed to make severance payments, advance compensations and to pay commissions for restructuring within the group. Under Bermuda law, directors are subject to election each year at the annual general meeting of the company, but there is no requirement that the chairman of the board of directors be elected by the shareholders. There is also no requirement under Bermuda law for shareholders to elect members of a company's compensation committee, or for shareholders to approve the compensation of the members of the board of directors or the company's management; the foregoing matters are typically determined by the company's board of directors. In addition, under Bermuda law there is no requirement to submit a written compensation report for approval to shareholders, and there are no general restrictions on severance payments, advance compensation or the payment of commissions for restructuring within the group. See "Risk Factors — Your rights as a shareholder of the Company will change as a result of the Redomestication. The Bye-laws grants certain powers to the board of directors that differs from our current articles of association. Such changes may adversely affect your rights as a shareholder of the Company." and "Agenda Item 1 — Redomestication of

the Company's corporate seat to Bermuda — Comparison of Corporate Law," where we describe material differences between the corporate law of Delaware, Switzerland and Bermuda relating to your rights as a shareholder. The form of Memorandum of Continuance and Bye-laws of Auris Medical (Bermuda) are filed as Appendix A and Appendix B, respectively, to this proxy statement/prospectus.

Upon effectiveness of the Redomestication, we will be a Bermuda company and it may be difficult for you to enforce judgments against us or our directors and executive officers.

Upon our continuance in Bermuda, we will be a Bermuda exempted company. As a result, the rights of holders of our common shares will be governed by Bermuda law and our Memorandum of Continuance and Bye-laws. The rights of shareholders under Bermuda law may differ from the rights of shareholders of companies incorporated in other jurisdictions. Many of our directors and the named experts referred to in this proxy statement/prospectus are not residents of the United States, and a substantial portion of our assets are located outside the United States. As a result, it may be difficult for investors to effect service of process on those persons in the United States or to enforce in the United States judgments obtained in U.S. courts against us or those persons based on the civil liability provisions of the U.S. securities laws. It is doubtful whether courts in Bermuda will enforce judgments obtained in other jurisdictions, including the United States, against us or our directors or officers under the securities laws of those jurisdictions or entertain actions in Bermuda against us or our directors or officers under the securities laws of other jurisdictions.

Your rights as a shareholder of the Company will change as a result of the Redomestication. The Bye-laws grants certain powers to the board of directors that differs from our current articles of association. Such changes may adversely affect your rights as a shareholder of the Company.

Because of the differences between Swiss law and Bermuda law, your rights as a shareholder will change if the Redomestication is completed. The Bye-laws grant certain powers to the board of directors that differ from our current articles of association. Generally, under Swiss law, shareholders are allowed to vote in matters related to an issuance of preferred shares or to alter the company's share capital by dividing, consolidating or sub-dividing the company's shares (including a reverse share split effected by consolidating our common shares (together with a corresponding increase in the par value thereof) in a ratio determined by the board of directors, while under Bermuda law, the board of directors have the power and authority to perform such acts without the shareholders' approval. Also, the presence and voting quorum requirements for certain shareholder resolutions under Swiss and Bermuda law differ in some instances. For example, the Bye-laws provide that, where certain business combination restrictions do not apply and the merger or amalgamation is approved by the board of directors, a merger or an amalgamation generally requires the approval of a majority of the votes cast at a general meeting at which the presence quorum is two or more persons present in person and representing in person or by proxy issued and outstanding voting shares. Whereas, under Swiss law, with certain exceptions, the approval of two thirds of the shares represented at the respective general meeting is required for a merger or an amalgamation. Additionally, under both Bermuda and Swiss law, shareholders may put proposals to the general meeting, but the exact framework and required shareholder and quorum requirements vary. Another matter that Bermuda and Swiss law differs is related to dividend payments. Under Swiss law, dividend payments are subject to the approval of the general meeting of shareholders. The board of directors may propose to shareholders that a dividend shall be paid but cannot itself authorize the distribution. Whereas, under Bermuda law, the board of directors may declare a dividend without shareholder approval, but a company may not declare or pay dividends if there are reasonable grounds for believing that: (i) the company is, or would after the payment be, unable to pay its liabilities as they become due; or (ii) that the realizable value of its assets would thereby be less than its liabilities. Also, the Bye-laws include anti-takeover provisions that our current articles of association do not contemplate. Such provisions give power and authority for the board of directors to require an increased majority for shareholder approval on a change of control. See "We have anti-takeover provisions in our proposed Bye-laws that may discourage a change of control." Such changes may adversely affect your rights as a shareholder of the Company. For a detailed discussion of these differences, see "Agenda Item 1 — Approval of the Redomestication — Comparison of Corporate Law."

Bermuda law differs from the laws in effect in the United States and may afford less protection to holders of our common shares.

Upon our continuance in Bermuda, we will be subject to the laws of Bermuda. As a result, our corporate affairs will be governed by the Companies Act, which differs in some material respects from laws typically applicable to U.S. corporations and shareholders, including the provisions relating to interested directors, amalgamations, mergers and acquisitions, takeovers, shareholder lawsuits and indemnification of directors. Generally, the duties of directors and officers of a Bermuda company are owed to the company only. Shareholders of Bermuda companies typically do not have rights to take action against directors or officers of the company and may only do so in limited circumstances. Class actions are not available under Bermuda law. The circumstances in which derivative actions may be available under Bermuda law are substantially more proscribed and less clear than they would be to shareholders of U.S. corporations. The Bermuda courts, however, would ordinarily be expected to permit a shareholder to commence an action in the name of a company to remedy a wrong to the company where the act complained of is alleged to be beyond the corporate power of the company or illegal, or would result in the violation of the company's memorandum of association or bye-laws. Furthermore, consideration would be given by a Bermuda court to acts that are alleged to constitute a fraud against the minority shareholders or, for instance, where an act requires the approval of a greater percentage of the company's shareholders than that which actually approved it.

When the affairs of a company are being conducted in a manner that is oppressive or prejudicial to the interests of some shareholders, one or more shareholders may apply to the Supreme Court of Bermuda, which may make such order as it sees fit, including an order regulating the conduct of the company's affairs in the future or ordering the purchase of the shares of any shareholders by other shareholders or by the company. Additionally, under our proposed Bye-laws and as permitted by Bermuda law, each shareholder has waived any claim or right of action against our directors or officers for any action taken by directors or officers in the performance of their duties, except for actions involving fraud or dishonesty. In addition, the rights of holders of our common shares and the fiduciary responsibilities of our directors under Bermuda law are not as clearly established as under statutes or judicial precedent in existence in jurisdictions in the United States, particularly the State of Delaware. Therefore, holders of our common shares may have more difficulty protecting their interests than would shareholders of a corporation incorporated in a jurisdiction within the United States.

Our proposed Bye-laws restrict shareholders from bringing legal action against our officers and directors.

Our proposed Bye-laws contain a broad waiver by our shareholders of any claim or right of action, both individually and on our behalf, against any of our officers or directors. The waiver applies to any action taken by an officer or director, or the failure of an officer or director to take any action, in the performance of his or her duties, except with respect to any matter involving any fraud or dishonesty on the part of the officer or director. This waiver limits the right of shareholders to assert claims against our officers and directors unless the act or failure to act involves fraud or dishonesty.

We have anti-takeover provisions in our proposed Bye-laws that may discourage a change of control.

Our proposed Bye-laws contain provisions that could make it more difficult for a third party to acquire us without the consent of our board of directors. These provisions provide for:

- directors only to be removed for cause;
- restrictions on the time period in which directors may be nominated;
- our board of directors to determine the powers, preferences and rights of our preference shares and to issue the preference shares without shareholder approval; and
- an affirmative vote of 66⅔% of our voting shares for certain "business combination" transactions which have not been approved by our board of directors.

These provisions could make it more difficult for a third party to acquire us, even if the third party's offer may be considered beneficial by many shareholders. As a result, shareholders may be limited in their ability to obtain a premium for their shares.

If the Redomestication is effected, legislation enacted in Bermuda in response to the European Union's review of harmful tax competition could adversely affect our operations.

During 2017, the European Union ("EU") Economic and Financial Affairs Council ("ECOFIN") released a list of non-cooperative jurisdictions for tax purposes. The stated aim of this list, and accompanying report, was to promote good governance worldwide in order to maximize efforts to prevent tax fraud and tax evasion. Bermuda was not on the list of non-cooperative jurisdictions, but did feature in the report (along with approximately 40 other jurisdictions) as having committed to address concerns relating to economic substance by December 31, 2018. In accordance with that commitment, Bermuda has enacted legislation that requires certain entities in Bermuda engaged in "relevant activities" to maintain a substantial economic presence in Bermuda and to satisfy economic substance requirements. The list of "relevant activities" includes carrying on as a business any one or more of: banking, insurance, fund management, financing, leasing, headquarters, shipping, distribution and service center, intellectual property and holding entities. At present, it is unclear what (if anything) Auris Medical (Bermuda) would be required to do in order to satisfy economic substance requirements in Bermuda, but to the extent we are required to increase our substance in Bermuda to satisfy such requirements, it could result in additional costs that could adversely affect our financial condition or results of operations. If we were required to satisfy economic substance requirements in Bermuda but failed to do so, we could face automatic disclosure to competent authorities in the EU of the information filed by the entity with the Bermuda Registrar of Companies in connection with the economic substance requirements and may also face financial penalties, restriction or regulation of its business activities and/or may be struck off as a registered entity in Bermuda.

BUSINESS

Overview

We are a clinical-stage biopharmaceutical company focused on the development of novel products that address important unmet medical needs in neurotology and mental health supportive care. We are focusing on the development of intranasal betahistine for the treatment of vertigo (AM-125) and for the prevention of antipsychotic-induced weight gain and somnolence (AM-201). These programs have gone through two Phase 1 trials and will move into proof-of-concept studies in 2019. In addition, we have two Phase 3 programs under development: (i) Keyzilen® (AM-101), which is being developed for the treatment of acute inner ear tinnitus and (ii) Sonsuvi® (AM-111), which is being developed for the treatment of acute inner ear hearing loss. Sonsuvi® has been granted orphan drug status by the FDA and the EMA and has been granted fast track designation by the FDA.

Recent Developments

Acquisition of orphan drug designation and rights to in-license patents related to betahistine

On December 6, 2018, we announced a strategic expansion for our intranasal betahistine development program. In two related transactions, we acquired an Orphan Drug Designation for betahistine in the treatment of obesity associated with Prader-Willi syndrome (PWS) and signed a binding letter of intent to in-license exclusive rights to two U.S. Patents relating to the use of betahistine for the treatment of depression and attention-deficit/hyperactivity disorder (ADHD), respectively. On January 15, 2019, we announced the closing of the acquisition of the Orphan Drug Designation and that the transfer of the designation to Auris Medical had been recorded by the FDA.

Positive Results From Second Phase 1 Clinical Trial With Intranasal Betahistine (AM-125)

On October 17, 2018, we announced positive results from the second Phase 1 trial evaluating intranasal betahistine in healthy volunteers. The study results demonstrated superior bioavailability over a range of four intranasal betahistine doses compared to oral betahistine, with plasma exposure being 6 to 29 times higher (p-value between 0.056 and $p < 0.0001$). Further, it confirmed the favorable safety profile of intranasal betahistine and showed that the treatment was well tolerated when administered three times daily for three days.

The randomized double blind placebo controlled Phase 1 trial with dose escalation enrolled a total of 72 healthy volunteers. One group of study participants received a single dose of intranasal betahistine or placebo and, following a wash-out period, three doses daily for three days. Single doses were escalated up to 60 mg, and repeated doses up to 40 mg. For the latter, the maximum tolerated dose based on local tolerability was determined at 40 mg. The other group of study participants received oral betahistine or placebo for reference. Pharmacokinetic parameters in blood plasma were determined for betahistine and its metabolites, and relative bioavailability for intranasal betahistine was calculated compared to oral betahistine 48 mg, which is the maximum approved daily dose as marketed worldwide (ex US). We plan to initiate two randomized double blind placebo controlled proof-of-concept studies with intranasal betahistine in the first quarter of 2019. In the planned TRAVERS, we plan to enroll patients suffering from acute vertigo following vestibular schwannoma resection.

We plan to initiate a Phase 2 randomized placebo-controlled clinical trial with AM-125 in the first quarter of 2019. The “TRAVERS” Phase 2 trial will enroll 138 patients suffering from acute vertigo following surgical removal of a vestibular schwannoma, a tumor growing behind the inner ear. It will be conducted in several European countries and potentially, Canada. The TRAVERS trial will have two parts: In Part A, five ascending doses of AM-125 or placebo, administered three times daily over a total of four weeks, will be tested in a total of 50 patients. In addition, oral betahistine 48 mg will be tested in 16 patients under open-label conditions for reference. Based on an interim analysis, two doses will be selected and tested in an estimated 72 patients in Part B.

Launch of AM-201 Program

On May 15, 2018, we announced the expansion of our intranasal betahistine development program beyond the treatment of vertigo into mental health supportive care indications. Under project code

AM-201, we intend to develop intranasal betahistine for the prevention of weight gain and drowsiness (somnolence), which are major side effects of many antipsychotic drugs. On November 20, 2018, we announced the results of our pre-Investigational New Drug ("IND") meeting on AM-201 with the FDA. In its written response, the FDA supported the planned conduct of a multiple dose Phase 1b proof-of-concept trial with AM-201 administered to healthy subjects in combination with olanzapine to evaluate the pharmacokinetics, pharmacodynamics and safety, and to establish proof-of-concept. Further, the FDA endorsed weight gain normalized to baseline body weight versus placebo as reasonable primary efficacy endpoint for a subsequent Phase 2 trial.

We expect to initiate the Phase 1b proof-of-concept trial in the first quarter of 2019. The trial will be conducted in Europe and will enroll 50 healthy volunteers who will receive either AM-201 or placebo concomitantly with olanzapine over four weeks.

Scientific Advice from the EMA on Development Plan and Regulatory Pathway for Sonsuvi®

On May 7, 2018, we announced that we had received positive Scientific Advice from the Committee for Medicinal Products for Human Use of the EMA related to the development plan and regulatory pathway for Sonsuvi®. The Scientific Advice (Protocol Assistance) had been requested by us following the results of the HEALOS Phase 3 trial. The EMA reviewed our proposed concept for a single pivotal trial with Sonsuvi® at a dose of 0.4 mg/mL in patients suffering from acute profound hearing loss, which builds to a large extent on the design and outcomes from HEALOS. The EMA endorsed the proposed trial design, choice of efficacy and safety endpoints, as well as the statistical methodology. In addition, the EMA provided important guidance on the regulatory path forward and the maintenance of Sonsuvi®'s orphan drug designation.

On August 30, 2018, we announced that we received feedback from a Type C meeting with the FDA related to the development plan and regulatory pathway for Sonsuvi®. The FDA reviewed our proposed concept for a placebo-controlled pivotal trial with Sonsuvi® at a dose of 0.4 mg/mL in patients suffering from acute profound hearing loss. The trial protocol builds to a large extent on the design and outcomes from HEALOS and also incorporates specific feedback provided by the EMA referenced above. In a written response, the FDA endorsed the proposed choice of primary and secondary efficacy endpoints, the safety endpoints, as well as the planned sample size and statistical methodology. In addition, the FDA provided important guidance on the regulatory path forward.

Identification of Potential Partners for Sonsuvi®

In early November 2018, we engaged JSB Partners LP, with offices in Boston, Munich and Zug, to identify potential partners for our Sonsuvi® program and to support us in negotiating potential partnering agreements.

Otonomy Ruling

On August 1, 2018, the United States Court of Appeals for the Federal Circuit reversed the USPTO Patent Trial and Appeal Board's determination of priority in our favor relating to the July 2015 USPTO declaration of patent interference (No. 106,030) involving our issued U.S. patent No. 9,066,865 and Otonomy's U.S. patent application No. 13/848,636. We believe that this ruling will not materially impact any of our development programs.

Nasdaq Listing Requirements

We are currently not in compliance with the quantitative listing standards of the Nasdaq Capital Market, which require, among other things, that listed companies maintain a minimum closing bid price of $1.00 per share. We failed to satisfy this threshold for 30 consecutive trading days and on July 30, 2018, we received a letter from Nasdaq indicating that we have been provided a period of 180 calendar days in which to regain compliance. We are in contact with Nasdaq regarding a plan to regain compliance. In the event that Nasdaq does not grant us an additional compliance period or we fail to regain compliance by the end of such additional compliance period, our board of directors will weigh the available alternatives to regain compliance, including pursuing a reverse share split by consolidating our common shares (together with a

corresponding increase in the par value thereof) in a ratio determined by the board of directors. In the event shareholders approve the Bye-laws, Auris Medical (Bermuda)'s board of directors could, after the Redomestication, effect a reverse share split without further shareholders approval, by consolidating our common shares (together with a corresponding increase in the par value thereof) in a ratio determined by the board of directors. However, there can be no assurance that we will be able to successfully resolve such noncompliance.

In addition to the minimum closing bid price requirement, we are required to comply with certain other Nasdaq continued listing requirements, including a series of financial tests relating to shareholder equity, market value of listed securities and number of market makers and shareholders. If we fail to maintain compliance with any of those requirements, our common shares could be delisted from Nasdaq's Capital Market. A delisting of our common shares is likely to reduce the liquidity of our common shares and may inhibit or preclude our ability to raise additional financing.

Amendment of Hercules Loan and Security Agreement

On April 5, 2018, we entered into an agreement with Hercules Capital, Inc. ("Hercules") whereby the terms of our Loan and Security Agreement (the "Loan and Security Agreement") with Hercules were amended to eliminate the $5 million liquidity covenant in exchange for a repayment of $5 million principal amount outstanding under the Loan and Security Agreement. As of September 30, 2018, CHF 2.1 million was the carrying amount under the Loan and Security Agreement.

January 2018 Offering of Common Shares and Warrants

On January 26, 2018, we entered into a purchase agreement with certain investors providing for the issuance and sale by us of 12,499,999 of our common shares. The common shares were offered pursuant to an effective shelf registration statement on Form F-3, which was initially filed with the Securities and Exchange Commission on September 1, 2015 and declared effective on September 10, 2015 (File No. 333-206710).

In a concurrent private placement, we issued to the same investors warrants to purchase up to 7,499,999 of our common shares in the aggregate. The warrants became exercisable immediately upon their issuance on January 30, 2018, at an exercise price of $0.50 per common share, and expire on January 30, 2025. Following the consummation of the Merger, the warrants became exercisable for an aggregate of 750,002 of our common shares (assuming we decide to round up fractional common shares to the next whole common share), at an exercise price of $5.00 per common share.

Committed Equity Financing

On May 2, 2018, we entered into the LPC Purchase Agreement with LPC. Pursuant to the LPC Purchase Agreement, LPC has agreed to subscribe for up to $10,000,000 of our common shares over the 30-month term of the LPC Purchase Agreement.

Pursuant to the LPC Purchase Agreement, so long as a registration statement covering the resale by LPC of the common shares that we issue to LPC pursuant to the LPC Purchase Agreement is available for use, we have the right, from time to time at our sole discretion over the 30-month period from and after June 15, 2018, the date of the satisfaction of the conditions in the LPC Purchase Agreement, to require LPC to subscribe for up to 250,000 of our common shares, subject to adjustments as set forth below (such maximum number of shares, as may be adjusted from time to time, the "Regular Purchase Share Limit"; each such purchase, a "Regular Purchase"); provided, however, that (i) the Regular Purchase Share Limit shall be increased to 300,000 of our common shares if the total number of outstanding common shares on the purchase date exceeds 10,000,000, (ii) the Regular Purchase Share Limit shall be increased to 350,000 of our common shares if the closing sale price of our common shares is not below $1.00 on the purchase date and the total number of outstanding common shares on the purchase date exceeds 12,500,000 and (iii) the Regular Purchase Share Limit shall be increased to 400,000 of our common shares if the closing sale price of our common shares is not below $1.00 on the purchase date and the total number of outstanding common shares on the purchase date exceeds 15,000,000. The Regular Purchase Share Limit is subject to proportionate adjustment in the event of a reorganization, recapitalization, non-cash dividend, stock split

or other similar transaction; provided, that if after giving effect to such full proportionate adjustment, the adjusted Regular Purchase Share Limit would preclude us from requiring LPC to subscribe for common shares at an aggregate purchase price equal to or greater than $100,000 in any single Regular Purchase, then the Regular Purchase Share Limit for such Regular Purchase will not be fully adjusted, but rather the Regular Purchase Share Limit for such Regular Purchase shall be adjusted as specified in the LPC Purchase Agreement, such that, after giving effect to such adjustment, the Regular Purchase Share Limit will be equal to (or as close as can be derived from such adjustment without exceeding) $100,000. We may not require LPC to purchase in any single Regular Purchase common shares having an aggregate purchase price greater than $1,000,000. We may not issue any of our common shares as a Regular Purchase on a date in which the closing sale price of our common shares is below $0.25 (subject to adjustment for any reorganization, recapitalization, non-cash dividend, stock split or other similar transaction). The purchase price for Regular Purchases shall be equal to the lesser of (i) the lowest sale price of our common shares on the applicable purchase date and (ii) the average of the three lowest closing sale prices of our common shares during the 10 business days immediately prior to the applicable purchase date, as reported on The Nasdaq Capital Market.

We also have the right, at our sole discretion, to require LPC to make tranche purchases of up to $2,000,000 in separate tranches of not less than $100,000 and up to $500,000 for each purchase, at a purchase price equal to the lesser of (i) $5.00 per common share or (ii) 96% of the purchase price, provided that (a) the closing price of the common shares is not below $1.00 and (b) the total number of outstanding common shares exceeds 12,500,000. We can deliver notice for a tranche purchase at any time, so long as at least 15 business days have passed since a tranche purchase was completed.

In all instances, we may not issue common shares to LPC under the LPC Purchase Agreement if it would result in LPC beneficially owning more than 4.99% of our outstanding common shares.

The LPC Purchase Agreement contains customary representations, warranties and agreements of the parties, certain limitations and conditions to completing future sale transactions, indemnification rights of LPC and other obligations of the parties. LPC has covenanted not to cause or engage in any manner whatsoever, any direct or indirect short selling or hedging of our common shares. We issued to LPC a cash commitment fee of $250,000 for entering into this commitment.

The net proceeds under the LPC Purchase Agreement will depend on the frequency and prices at which we issue our common shares to LPC. We expect that any proceeds received by us from such issuances to LPC will be used for working capital and general corporate purposes. We have the right to terminate the LPC Purchase Agreement at any time for any reason upon one business day's written notice to LPC. In the event that the Redomestication is effected, the LPC Purchase Agreement will automatically terminate. In order to maintain this source of funding we will need to negotiate a new purchase agreement with LPC. We cannot be certain that we will be able to negotiate a new purchase agreement with the same terms and conditions, or at all.

Since September 30, 2018, we have sold 1,750,000 of our common shares for an aggregate offering price of $1.0 million pursuant to the LPC Purchase Agreement.

July 2018 Offering of Common Shares and Warrants

On June 28, 2018, an extraordinary general meeting of shareholders approved an ordinary share capital increase and certain changes to our articles of association to increase our authorized share capital and our conditional share capital for financing purposes (collectively, the "Capital Increase"). On July 17, 2018, the Company closed its registered offering of 17,948,717 common shares, Series A warrants to purchase 6,282,050 common shares and Series B warrants to purchase 4,487,179 common shares. We refer to such offering of common shares as the "July 2018 Registered Offering."

Since the July 2018 Registered Offering, certain Series A warrant holders exercised their warrant shares to purchase 2,904,518 common shares of the Company and certain Series B warrant holders exercised warrant shares to purchase 2,864,422 common shares.

2018 Registered Direct Offerings of Common Shares

On November 27, 2018 and December 11, 2018, we entered into purchase agreements with FiveT Capital AG, providing for the issuance and sale by us of an aggregate of 3,315,000 of our common shares for an aggregate purchase price of $1.6 million in two separate registered direct offerings.

"At-the-Market" Offering Program

On November 30, 2018, we entered into the A.G.P. Sales Agreement with A.G.P. Pursuant to the terms of the A.G.P. Sales Agreement, we may offer and sell our common shares, from time to time through A.G.P. by any method deemed to be an "at-the-market" offering as defined in Rule 415(a)(4) promulgated under the Securities Act. Pursuant to the A.G.P. Sales Agreement, we may sell common shares up to a maximum aggregate offering price of $25.0 million.

In the event that the Redomestication is effected, we will need to amend the A.G.P. Sales Agreement before we can sell additional common shares to A.G.P. We cannot be certain that we will be able to negotiate an amendment with the same terms and conditions, or at all.

As of the date of this proxy statement/prospectus, we have sold 2,130,670 of our common shares for an aggregate offering price of $1.1 million pursuant to the A.G.P. Sales Agreement.

Corporate Information

We are a share corporation organized under the laws of Switzerland. We began our current operations in 2003. On April 22, 2014, we changed our name from Auris Medical AG to Auris Medical Holding AG and transferred our operational business to our newly incorporated subsidiary Auris Medical AG, which is now our main operating subsidiary.

On March 13, 2018, in order to effect a 10:1 reverse share split, Auris Medical Holding AG merged into Auris Medical NewCo Holding AG (the "Merger"), a newly incorporated, wholly-owned Swiss subsidiary ("Auris NewCo") following shareholder approval at an extraordinary general meeting of shareholders held on March 12, 2018. Following the Merger, Auris NewCo, the surviving company had a share capital of CHF 122,347.76, divided into 6,117,388 common shares with a nominal value of CHF 0.02 each. Pursuant to the Merger, our shareholders received one common share with a nominal value of CHF 0.02 of Auris NewCo for every 10 common shares in Auris Medical Holding AG held prior to the Merger, effectively resulting in a "reverse share split" at a ratio of 10-for-1. Auris NewCo changed its name to "Auris Medical Holding AG" as part of the consummation of the Merger, effective March 13, 2018. On March 14, 2018, the common shares of Auris NewCo began trading on The Nasdaq Capital Market under the trading symbol "EARS."

Our principal office is located at Bahnhofstrasse 21, 6300 Zug, Switzerland, telephone number +41 (0)41 729 71 94. We maintain a website at www.aurismedical.com where general information about us is available. Investors can obtain copies of our filings with the SEC from this site free of charge, as well as from the SEC website at www.sec.gov. We are not incorporating the contents of our website into this proxy statement/prospectus.

Business overview

Strategy

Our goal is to become the leading biopharmaceutical company focused on developing and commercializing novel therapeutics to treat neurotology and CNS disorders. The key elements of our strategy to achieve this goal are:

- ***Target disorders that have a defined pathophysiology and that are amenable to treatment.*** We are focusing on disorders for which the pathophysiology is defined, can be effectively targeted and where affected patients seek medical attention proactively.

- ***Use drug delivery techniques and proprietary drug formulations for effective, safe and rapid targeted administration.*** We are developing treatments for neurotology disorders based on targeted drug delivery. Where the target is inside the inner ear, such as in case of acute inner ear hearing loss or tinnitus, we employ intratympanic injections into the middle ear. This short outpatient procedure allows us to deliver therapeutic concentrations of drug in a highly targeted fashion with only minimal systemic exposure. We are using proprietary, fully biocompatible and biodegradable gel

formulations for optimum middle ear tolerance and effective diffusion of active substances into the inner ear. Where the target is localized not only in the inner ear, but also in the brain, as in the case of vertigo, we are using a spray formulation for intranasal drug delivery to reach it more effectively than with oral administration.

- ***Leverage products into additional therapeutic indications.*** We consider our intranasal betahistine program as a platform on which various indications can be developed. The program started with project AM-125 for the treatment of acute vertigo and has been expanded with project AM-201 to address also the prevention of antipsychotic-induced weight gain. We see additional opportunities in other indications and seek to explore those for further indication expansions.

- ***Build an efficient commercial infrastructure to maximize the value of our product candidates.*** We intend to build commercial operations in select markets. In those markets, we expect our commercial operations to include specialty sales forces targeting ENTs and specialists in neurotology both in hospitals and in private practice. In other markets, we expect to seek partnerships that would maximize our products' commercial potential.

The Inner Ear

We have focused our drug discovery and development efforts on targeting the inner ear, which is comprised of the cochlea, the organ of hearing, and the vestibular system, the organ of balance. The snail-shaped cochlea is the sensory organ at the periphery of the auditory system, which transmits sound along the auditory pathway up to the brain for hearing. Acute insults to the cochlea from a variety of sources — for example, loud noise, infection or insufficient blood supply — may lead to excessive levels of glutamate, the principal neurotransmitter in the cochlea as well as other pathological processes. This in turn may damage cochlear hair cells, which tune and amplify sound inside the cochlea or convert mechanical movement into neural signals, as well as cochlear neurons. Such damage may result in the symptoms of inner ear hearing loss and/or inner ear tinnitus that can be transitory as natural repair mechanisms set in or that become permanent when hair cells or neurons die or are permanently injured.

Because the cochlea is located deep inside the head and because it is separated from the middle ear by a combination of bone and membranes, the interior of the cochlea is a challenging location for drug delivery. We have chosen to deliver certain of our products via intratympanic injection across the ear drum (also known as the tympanic membrane) into the middle ear cavity. By formulating our products with biocompatible gels, we facilitate the diffusion of active substances across the round window membrane into the cochlea at clinically meaningful concentrations.

The vestibular system communicates with the cochlea and consists of three semi-circular canals and the vestibule. It is responsible for the sensations of balance and motion. The vestibular system uses the same kinds of fluids and detection cells (hair cells) as the cochlea and sends information to the brain regarding the altitude, rotation, and linear motion of the head. The vestibular system works with the visual system to keep objects in view when the head is moved. Joint and muscle receptors are also important in maintaining balance. The brain receives, interprets, and processes the information from all these systems to create the sensation of balance.

When vestibular input from each ear is equal, the system is in balance, and there is no sense of movement. When inputs are unequal, the brain interprets this as movement. As a result, compensatory eye movements and postural adjustments occur to maintain balance. However, when some pathology (e.g., inflammation or trauma) disrupts signaling unilaterally, the result is an imbalance in vestibular input that can lead to vertigo.

Market

Inner ear disorders, including hearing loss, tinnitus, Meniere's Disease and balance disorders, are common and often inter-related conditions. Chronic inner ear disorders such as tinnitus and hearing loss are highly prevalent. According to the National Institute on Deafness and Other Communication Disorders, or NIDCD, approximately 10% of the U.S. adult population, or about 25 million Americans,

have experienced tinnitus lasting at least five minutes in the past year. Additionally, according to a 2016 publication by Bhatt et al. in the journal JAMA Otolaryngology — Head and Neck Surgery, 21.4 million (9.6%) U.S. adults experienced tinnitus in the past 12 months.

The NIDCD also reports that 37.5 million Americans, or 15% of the adult U.S. population, report having some trouble hearing. Epidemiological studies reveal comparable prevalence rates for Europe. Additionally, according to a 2016 publication by Hoffman et al. in the journal JAMA Otolaryngology — Head and Neck Surgery, the annual prevalence of speech-frequency hearing loss among adults aged 20 to 69 years was 14.1% (27.7 million) in the 2011 – 2012 period. Furthermore, according to the NIDCD, more than four out of 10 Americans, at some point in their lives, experience an episode of dizziness significant enough to see a doctor. Approximately 615,000 individuals in the United States are currently diagnosed with Meniere's disease and 45,500 cases are newly diagnosed each year.

According to a 2011 publication by Hall et al. in the journal BMC Health Services Research, among the tinnitus patients seen by physicians who reported seeing at least one tinnitus patient in the previous three months, approximately 36% of patients sought medical treatment during the first three months following the onset of the disorder.

The market for ear disorders is underserved despite the fact that according to a 2007 report by the consulting firm NeuroInsights, hearing loss ranks among the top ten neurologic disorders by worldwide prevalence, ranking above attention deficit disorders, Alzheimer's disease and multiple sclerosis. There are three main reasons for this:

- ***Inner ear physiology.*** It has been extremely challenging for pharmaceutical companies to deliver drugs at effective concentrations to the inner ear. Like the eye, the inner ear is a protected space. Systemically administered drugs such as intravenous or oral formulations in doses high enough to reach effective inner-ear concentrations often bring unacceptable systemic toxicity.
- ***Heterogeneity of inner ear disorders.*** Hearing loss, tinnitus and vertigo are symptoms of many different underlying etiologies, and they manifest themselves in many different ways. For example, tinnitus may be provoked by such different proximal causes as whiplash injury, excessive noise exposure, the flu or even certain dental problems. In some cases, the tinnitus originates inside the cochlea, but then becomes "centralized," that is, the phantom sound persists even long after the initial source of the sensation has been removed. In case of vertigo, possible triggers include infection, inflammation, surgical trauma, disturbances of inner ear fluid balance or debris inside the inner ear. There has been a dearth of knowledge about the pathophysiology of tinnitus, hearing loss and vertigo, which has hindered the pharmaceutical industry in pursuing therapeutics in this area.
- ***Lack of clinical trial paradigms.*** Historically, there have been challenges regarding the clinical endpoints used in measuring changes in tinnitus. Since tinnitus usually is perceived only by the patient affected by it, there is no direct way of measuring it. Like pain, tinnitus assessments have to rely on subjective endpoints. Tinnitus assessments consist either of psychoacoustic measures, performed by audiologists and other hearing specialists and sometimes considered as "semi-objective," or they are based on PROs. Unlike in pain, there has been a lack of guidelines and validation work on these PROs, and the relevance and reliability of psychoacoustic measures as efficacy outcome variables have been questioned.
- ***Challenges with bioavailability.*** Betahistine, the active substance of AM-125 and also AM-201, has been used for decades for the treatment of vertigo. However, when administered orally, only small quantities of the drug actually reach the blood stream and can be distributed to the inner ear and the brain due to rapid and pronounced first pass metabolism. As a consequence of the low bioavailability, there has been significant variability in therapeutic outcomes.

For these reasons, the industry's discovery and development of novel therapies for inner ear disorders has lagged far behind efforts in other therapeutic areas.

We are addressing each of these issues with our approach to developing therapeutics targeting the inner ear. Using targeted drug delivery to the inner ear reduces systemic exposure to our product candidates. We target specific types of tinnitus, hearing loss and vertigo that are addressable with drug-based therapies. We have worked with regulatory agencies to develop and validate acceptable clinical trial paradigms.

Our Localized Delivery Solution for the Inner Ear for the Treatment of Tinnitus and Hearing Loss

The inner ear is a protected part of the body, analogous to the eye. It is hidden in the temporal bone, behind the middle ear and the ear drum. In addition, it is very tiny: the cochlea measures about the size of the fingernail on the little finger. Therefore, therapeutically targeting the inner ear is not easy. There is currently no FDA or EMA approved drug therapy for the treatment of tinnitus or hearing loss on the market.

The blood labyrinth barrier is a major physiological divider separating the inner ear from systemic circulation, critically preserving the inner ear's microenvironment. Systemic drug dose levels capable of having a therapeutic effect on the inner ear are often high enough to cause adverse side effects.

An alternative approach is to administer drugs locally by intratympanic injection to maximize efficacy and minimize systemic side effects. With intratympanic administration, the drug is injected via a needle through the anesthetized ear drum into the middle ear cavity. The drug then diffuses across the semi-permeable round window membrane (RWM) into the inner ear. Our lead product candidates are administered by intratympanic injection. We chose this approach after thorough evaluation of all available alternatives because it offers the optimal combination of access, convenience, physician familiarity and safety. We formulated our product candidates specifically with intratympanic delivery in mind.

One of the key shortcomings of current intratympanic approaches is the use of injectable solutions that may easily drain off via the Eustachian tube, thus preventing or reducing effective diffusion into the cochlea. With our proprietary gel formulations for intratympanic injections we overcome this "draining off," facilitate contact with the RWM and achieve effective diffusion into the cochlea.

Both Keyzilen® and Sonsuvi® are formulated in a viscous gel of sodium hyaluronate that is biocompatible, biodegradable, and isotonic (that is, having the same salt concentration and therefore not causing any pressure build up on either side of the RWM). The gel has a physiologic or near-physiologic pH which helps minimize potential irritation to the ear. We selected its viscosity in a way that the free movement of the ossicular chain, which transfers the vibrations of the eardrum to the inner ear, is not impacted. The presence of highly viscous gels in the middle ear may cause transient conductive hearing loss.

In addition, in the case of Sonsuvi®, we are employing D-TAT, a peptidic active transporter technology that allows the transport of a large molecule to the inner ear that would normally be blocked by the RWM. This novel use of D-TAT brings peptides not only behind the RWM but inside cells in the inner ear. To our knowledge, we are the first company to be delivering intracellular peptides to the inner ear using an active transporter such as D-TAT.

The intratympanic injection procedure by which our therapeutics are delivered to the RWM is a minimally invasive procedure that is relatively simple to perform by an experienced ENT specialist. Most ENT physicians and neurotologists have a high degree of comfort with intratympanic injection and it is well-accepted by patients. A billable procedure, intratympanic injection is routinely reimbursed under a broader reimbursement code. For the injection, patients lie on a stretcher or on a reclined exam chair, treated ear up; the injection is performed under local anesthesia of the eardrum by an ENT specialist using a microscope. Following the procedure, patients rest for 20 to 30 minutes to ensure maximum physical contact of the drug with the RWM. The tympanic membrane heals rapidly, usually within a few days, and the procedure may be performed several times. Often performed in children suffering from ear infections, the reversible opening of the eardrum is one of the most frequent ENT procedures.

Our Targeted Delivery Solution for the Treatment of Vestibular Disorders

In vestibular disorders, the target for pharmacologic intervention may not only be in the inner ear, but also in central parts of the vestibular system, i.e., the brain. In such case, a treatment may be best delivered systemically, provided that the active substance can reach these targets. Intranasal administration is a non-invasive route for drug delivery, which allows for drugs to be absorbed into the systemic circulation through the nasal mucosa. This route may be used in a range of acute or chronic conditions requiring considerable systemic exposure. It offers advantages such as ease of administration, rapid onset of action, and avoidance of first-pass metabolism.

Our Product Candidates

The following table summarizes our product development pipeline[(1)]:

Product	Indication	Preclin.	Phase 1	Phase 2	Phase 3	Next Key Milestones
AM-125 Betahistine	Vertigo					Start Phase 2 trial (Q1 2019)
AM-201 Betahistine	Antipsychotic-induced weight gain					Start PK/PD study (Q1 2019)
Sonsuvi® (AM-111) Brimapitide	ASNHL (sudden deafness)					Partnering
Keyzilen® (AM-101) Esketamine	Acute inner ear tinnitus					Reconfirming efficacy in Proof-of-concept study with objective tinnitus diagnostic
AM-102 Undisclosed	Tinnitus					Select lead compound

(1) Dates of key milestones are indicative and subject to change.

Keyzilen® in Tinnitus

Our clinical program with Keyzilen®, Esketamine gel for injection, is in Phase 3 clinical trials in acute inner ear tinnitus. Esketamine is a potent, small molecule non-competitive NMDA receptor antagonist. Keyzilen® is formulated in a biocompatible gel and delivered via intratympanic injection. It has demonstrated a favorable safety profile and positive effect on PROs associated with tinnitus in two Phase 2 clinical trials. The Phase 3 clinical development program comprised two pivotal clinical trials with highly similar design, one in North America (TACTT2) and one in Europe, which we refer to as TACTT3.

Tinnitus

Tinnitus, frequently perceived as a ringing in the ears, is the perception of sound when no external sound is present. Similar to pain, it is an unwanted, unpleasant and thus distressing sensation. Tinnitus may result in further symptoms such as inability to concentrate, irritability, anxiety, insomnia, and clinical depression. In many cases, tinnitus significantly impairs quality of life and affects normal day-to-day activities. According to the American Tinnitus Association, approximately 16 million patients in the United States have tinnitus symptoms severe enough to seek medical attention and about two million patients cannot function on a normal day-to-day basis. In addition, tinnitus is now the number one service-connected disability for all veterans, before hearing loss, and annual service-connected disability payments for tinnitus to veterans from all periods of service were expected to exceed $2.75 billion by the end of 2016.

Tinnitus is categorized as acute during the first three months and chronic when it persists for more than three months. The distinction between acute and chronic is based on the clinical observation that spontaneous recovery or complete remission of tinnitus is much more likely to occur in the first days, weeks and months following its onset. The chances of spontaneous recovery decline exponentially as the acute phase progresses. In the chronic stage, improvement is much more unlikely, and the therapeutic focus shifts from curing to managing the disorder. In some cases, tinnitus originates inside the cochlea, or the periphery of the auditory system, but then becomes “centralized,” that is, the phantom sound persists even long after the initial source of the sensation has been removed.

Tinnitus is a symptom that can be triggered by a variety of diseases or incidents such as noise trauma, infection, inflammation, vascular problems, temporomandibular joint dysfunction, head trauma or whiplash injury. In the majority of cases the tinnitus originates in the cochlea, but the precise mechanisms of tinnitus generation are still the subject of considerable debate and remain to be fully elucidated. In our development we are focusing on one particular, well-defined type of tinnitus generation based on glutamate excitotoxicity.

Acoustic trauma and other insults to the inner ear may trigger increased levels of extra-cellular glutamate, which in turn cause excessive activation of cochlear NMDA receptors. This process results in damage or killing of sensory cells and is thought to be responsible for abnormal spontaneous "firing" of auditory nerve fibers, which may be perceived as tinnitus. Under normal circumstances, the NMDA receptors are thought to play no role in the auditory nerve's transmission of nerve pulses that carry sound information. In case of a trauma such as excessive sound exposure these receptors may become pathologically active, and thus tinnitus is triggered.

Current Therapies and Unmet Need

Tinnitus treatments may be categorized according to whether they treat the underlying cause or provide symptomatic relief. It is rarely possible to treat the underlying cause. When it is possible, treatment often involves a surgical procedure to resect tumors or vascular abnormalities. In contrast, treatments to provide symptomatic relief are highly diverse, reflecting the general lack of understanding of the underlying pathophysiology.

Currently, the most widely employed treatment options include counseling, cognitive behavioral therapy, various forms of sound therapies, tinnitus retraining therapy, or TRT, herbal and vitamin supplements, ginkgo biloba, vasodilators, steroids, benzodiazepines and tricyclic antidepressants.

Sound-based therapies and TRT are some of the most commonly employed treatments for tinnitus. TRT is a non-pharmacological intervention that employs low-level sound emitted by a so-called "masking device" worn behind or in the ear. TRT also incorporates patient counseling to help habituate patients to their tinnitus. In those cases in which it is effective, TRT takes one to two years before patients "learn" to ignore tinnitus without the aid of a masking device. TRT can cost $2,500 to $3,000, including the masking devices. After an initial period of enthusiasm in the 1980s, masking devices declined in popularity among clinicians because it became clear that many patients who agreed to try them were nonusers six months later. While classic sound based therapies are based on broadband sound, newer therapies use sound individually tailored to the hearing loss and tinnitus characteristics.

Although there are no approved drugs in the United States for the treatment of tinnitus, there is widespread off-label use of drugs approved for other indications. The U.K. Royal National Institute for the Deaf reports that more than three million prescriptions are written each year in the United States and Europe for drugs that purport to offer tinnitus relief, drugs for which there is no proven efficacy.

The local anesthetic and antiarrhythmic drug lidocaine is the only substance to date that is known to attenuate tinnitus, albeit only temporarily. This illustrates that tinnitus can be addressed using pharmacological intervention. However, lidocaine causes severe vertigo and other side effects, preventing its widespread clinical use.

Our Solution — Keyzilen® (AM-101)

Therapeutic rationale for Keyzilen® in tinnitus

The API of Keyzilen® is Esketamine hydrochloride, a well-known small molecule non-competitive NMDA receptor antagonist. As described above, acoustic trauma and other insults to the inner ear have been shown in animal studies to activate cochlear NMDA receptors. The antagonist effect of Esketamine towards the NMDA receptor aims to suppress the aberrant activity of the auditory nerve and thus diminish tinnitus.

The NMDA receptor was first validated as a target for the treatment of tinnitus using an animal behavioral model of tinnitus triggered by salicylate, the active substance of aspirin. Salicylate is known to trigger temporary tinnitus when administered in high doses. The animal model demonstrated that local administration of different NMDA antagonists to the inner ear allowed for suppression of salicylate induced tinnitus. Together with INSERM, we developed a much more clinically relevant model of tinnitus induced by AAT. Unlike salicylate-induced tinnitus, AAT triggers glutamate excitotoxicity and may lead to irreversible damage to sensory cells. It does not result in tinnitus in all cases, but where it sets in, it may be permanent. In our pre-clinical trials, we demonstrated that Keyzilen® was able to suppress this type of tinnitus. Further pre-clinical work demonstrated that tinnitus could be suppressed even when drug was administered after the onset of tinnitus.

Toxicology and tolerability studies confirmed that Keyzilen® had no impact on hearing, even at much higher doses than those needed for suppressing tinnitus. Animal biodistribution studies showed rapid diffusion of the active substance into the cochlea. Concentrations decreased over several days due to clearance.

Ketamine has been used clinically for decades as an anesthetic and analgesic. Esketamine is the S-enantiomer of Ketamine and was introduced in a small number of markets outside the United States as a more potent NMDA receptor antagonist with more favorable side effects than racemic Ketamine. The development of Keyzilen® has benefitted from the long-standing clinical use of Ketamine and Esketamine as well as the wealth of published pharmacology, pharmacokinetic and safety data. We are using Esketamine in doses that result in systemic exposure several orders of magnitude lower than those seen when Esketamine is used as an anesthetic at clinically safe doses.

Tinnitus endpoints

Given the lack of existing tinnitus treatments, there have been no fully validated or universally accepted outcome measures for clinical trials. There are two fundamental types of efficacy outcome variables. PROs such as the visual or numerical rating of tinnitus loudness or tinnitus questionnaires provide direct subjective measures of tinnitus and its impact on sleep, relaxation, communication, emotions, social interactions and other factors. For example, patients are asked a single question to rate the loudness of their tinnitus "right now" on a scale from 0 ("no tinnitus heard") to 10 ("tinnitus extremely loud"). Among several tinnitus questionnaires, the 25 item TFI is one of the most recent. It was developed and validated broadly in line with the PRO guidelines of the FDA and was introduced in 2011 by Meikle et al. following extensive validation work, as described in the journal Ear & Hearing. Alternatively, measures commonly referred to as psychoacoustic may be performed by an audiologist, which is why they are considered "semi-objective." They seek to determine how loud a masking sound has to be to cover the tinnitus (minimum masking level, or MML) or how loud the tinnitus is compared to reference sound (equal loudness match).

In our Phase 2 clinical trials, PROs showed good responsiveness and consistent results, whereas psychoacoustic measures proved highly variable and unreliable. Therefore, following discussions with the FDA and EMA, it was agreed that our Phase 3 clinical program for Keyzilen® would be based on PROs with the improvement of subjective tinnitus loudness being defined as the primary efficacy endpoint. As part of the SPA with the FDA, it was agreed that improvement as measured by the TFI questionnaire would serve as a co-primary efficacy endpoint in our TACTT2 trial in order to confirm the clinical meaningfulness of a reduction in tinnitus loudness.

Keyzilen® Clinical Development

Phase 1/2

We conducted the first clinical evaluation of Keyzilen® in a Phase 1/2 double blind, randomized, placebo-controlled trial that included dose escalation from 0.03 to 0.81 mg/mL. The trial enrolled 24 patients suffering for up to three months from severe or disabling permanent inner ear tinnitus caused by AAT or sudden deafness (also called idiopathic sudden sensorineural hearing loss, or ISSNHL) and after unsuccessful steroid treatment. The primary objective of the trial was to evaluate the safety of intratympanically delivered Keyzilen®. This first clinical trial showed that single doses of intratympanically administered Keyzilen® were well tolerated up to the highest tested dose of 0.81 mg/mL. Only small traces of Esketamine and its primary metabolite were detected in blood samples within the first hours following treatment administration.

Phase 2

Following successful completion of our Phase 1/2 trial, we conducted two multi-center Phase 2 trials, one in Europe (Treatment of Acute Inner Ear Tinnitus 0 or TACTT0) and the other in Europe and the United States (which we refer to as TACTT1).

TACTT0

TACTT0 was conducted at 28 European sites between March 2009 and May 2011. This trial was a double-blind, randomized, placebo controlled, multiple dose, parallel group, Phase 2 clinical trial. It enrolled patients with persistent inner ear tinnitus as a result of AAT, otitis media (OM), or ISSNHL, occurring not more than three months prior, and with a MML of at least 5 dB. Trial participants received three intratympanic administrations of Keyzilen® at dose levels of either 0.27 mg/mL or 0.81 mg/mL or placebo over three consecutive days. A total of 248 patients were randomized (approximately eighty per treatment group). The improvement in the MML was the primary efficacy endpoint. The improvement in subjective tinnitus loudness and in tinnitus annoyance were co-primary efficacy endpoints. Trial outcomes are described by van de Heyning and colleagues in a 2014 article in Otology & Neurotology.

In this trial, Keyzilen® was well tolerated and had no negative impact on hearing. Adverse events were mostly local and related primarily to anticipated temporary changes in tinnitus loudness and muffled hearing following the intratympanic injection procedure. These effects usually resolved with closure of the ear drum.

Overall, the trial failed to demonstrate a treatment benefit based on the change in the MML as there was no difference in outcomes between treatment groups. However, post-hoc efficacy analysis. based on PROs in the subgroup of patients with tinnitus caused by AAT or OM (n=118), that is, patients with well-established cochlear origin of tinnitus, demonstrated superiority of the high dose of Keyzilen® with respect to placebo for the change in the co-primary efficacy endpoint tinnitus loudness, sleep difficulties (e.g., falling asleep), and the THI-12 questionnaire from baseline to Day 90. When restricting the OM + AAT population to unilateral cases (71% of the subgroup), the treatment effects became more pronounced in these measures; in addition, the improvement in tinnitus annoyance also became nominally significant. The improvement in PROs was gradual over the 90 day observation period. At Day 90 the mean improvement in tinnitus loudness was 48% in the Keyzilen® 0.81 mg/mL group compared to 9% in the placebo group. 64% of patients in the high dose group rated their tinnitus severity at Day 90 compared to baseline as “much improved” or “very much improved”, compared with 34% of patients in the placebo group. The majority of placebo treated patients reported only “somewhat improved” tinnitus severity. The improvements were dose dependent as the low-dose of Keyzilen® overall showed improvement between the high-dose and the placebo groups.

In case of ISSNHL related tinnitus, no treatment effects were evident as an unexpectedly high rate of spontaneous remission and substantial heterogeneity in outcomes were observed. Given the high variability and the uncertainty over the precise trigger of the tinnitus in ISSNHL, we decided to continue clinical development exclusively in tinnitus with established cochlear origin (such as AAT and OM).

TACTT1

TACTT1, our second double-blind, randomized, placebo-controlled Phase 2 clinical trial, was conducted between 2011 and 2013 in the United States, Belgium, Germany and Poland to complement the TACTT0 trial, notably by evaluating efficacy trends with different treatment schemes and by obtaining additional data on concentrations of Esketamine and its primary metabolite in the bloodstream.

Enrollment consisted of 85 patients suffering from acute inner ear tinnitus following AAT or OM. Tinnitus after barotrauma and middle ear surgery were added as traumatic cases in addition to AAT.

Patients received single (Cohort 1) or multiple (Cohort 2: three injections over two weeks) doses of Keyzilen® at a dose level of 0.81 mg/mL or placebo. Unlike TACTT0, this trial allowed bilateral treatment where tinnitus was present in both ears. Subjective tinnitus loudness was selected as the primary efficacy measure, while the highly variable MML was monitored as a secondary read out.

As described by Staecker and colleagues in an article in Audiology & Neurotology in 2015, TACTT1 further confirmed the safety and tolerability outcomes observed in the preceding trials. It further demonstrated the gradual improvement in PROs in Keyzilen® treated groups that had already been observed in TACTT0. The primary efficacy analysis showed no statistically significant trend for improvement in subjective tinnitus loudness related to the number of injections.

When comparing the improvement in tinnitus loudness in patients with unilateral tinnitus following traumatic injury to the cochlea or OM, treatment effects in TACTT1 were smaller than in TACTT0. The observed differences suggest that repeated and concentrated application of Keyzilen® and hence concentrated inhibition of cochlear NMDA receptors provides superior treatment benefits. Over the two Phase 2 clinical trials, Keyzilen® 0.81 mg/mL showed a statistically significant improvement in the AAT and OM group of patients when compared against placebo.

As in the TACTT0 trial, psychoacoustic measures such as MML were marked by high variability, confirming their limited suitability and reliability as efficacy outcome measure.

Keyzilen® Phase 3 Clinical Program

We have conducted two pivotal trials with Keyzilen® with highly similar designs, one in North America (TACTT2) and one in Europe (TACTT3). TACTT2 enrolled 343 patients, while TACTT3 Stratum A (Europe) has randomized 372 patients, both during the acute stage. Both trials were designed as a randomized, double-blind, placebo-controlled trial in acute inner ear tinnitus following traumatic cochlear injury or otitis media. Trial participants received three injections of Keyzilen® 0.87 mg/mL or placebo in a 3:2 ratio over three to five days and were followed for 84 days. The TACTT2 trial was conducted primarily in North America, the TACTT3 trial was conducted exclusively in Europe.

In addition, TACTT3 Stratum B explored the potential efficacy of Keyzilen® during the post-acute stage (tinnitus onset between three and 12 months) since data from our Phase 2 clinical program suggested that Keyzilen® might be effective beyond the three month acute stage. An Independent Data Review Committee conducted an interim analysis after enrollment of 150 patients. The interim analysis showed positive efficacy signals, with higher activity levels observed in the early post-acute stage (three to six months) compared to the late post-acute stage (six to 12 months). Based on recommendations from the Independent Data Review Committee, TACTT3 Stratum B continued solely with enrollment of patients with tinnitus onset three to six months prior. In total, 369 patients were randomized in TACTT3 Stratum B pre- and post-interim analysis.

Two further trials, AMPACT1 and AMPACT2 (Keyzilen® in the Post-Acute Treatment of Peripheral Tinnitus) were nine-month open label extension trials conducted at the same sites as for TACTT2 and TACTT3. These extension trials were open to participants who completed the TACTT2 or the TACTT3 trial (the latter until summer 2016) and evaluated the safety and local tolerance of up to three treatment cycles, each with three repeated doses of Keyzilen® 0.87 mg/mL.

The extension trials were designed in response to the FDA's request for safety data from chronic intermittent use by tinnitus patients in support of a NDA filing. Although we do not have any plans to seek a label for such use, the FDA considered such unintended use likely to occur.

On August 18, 2016, we announced that the Phase 3 TACTT2 clinical trial did not meet the two co-primary efficacy endpoints of statistically significant changes in tinnitus loudness and the TFI questionnaire compared to placebo.

Baseline values for tinnitus loudness and TFI were 6.44 and 52.4 points in the Keyzilen® group, and 6.47 and 50.2 points in the placebo group. Treatment with Keyzilen® resulted in a reduction in tinnitus loudness of 0.63 points, compared to a reduction of 0.80 points for placebo (p-value of 0.321). With respect to tinnitus burden, treatment with Keyzilen® resulted in a 9.67 point reduction, as measured by the TFI, compared to a reduction of 10.63 points for placebo (p-value of 0.565). A reduction of 13 points as measured by the TFI was defined as clinically meaningful by the developers of the TFI. By convention, a p-value that is less than 0.05 is considered statistically significant.

Keyzilen® was well tolerated with no drug-related serious adverse events. The trial's primary safety endpoint, incidence of clinically meaningful hearing deterioration, was low with no statistically significant difference from the placebo group (p-value of 0.82), supporting the safety profile of Keyzilen®.

We believe we have identified two principal sources for the outcome: (i) the high frequency of tinnitus loudness ratings over an extended period of time and (ii) an unexpectedly high level of variability in outcomes among study sites. We believe the daily capture of tinnitus loudness and annoyance may have

caused a number of patients to excessively focus on their tinnitus symptoms. With respect to variability, our analysis subsequent to the unblinding of the trial data has shown positive outcomes at numerous sites, including many of the high enrolling study centers, but inconclusive or contradictory outcomes at other sites.

However, the TACTT2 trial data show treatment effects on TFI in favor of Keyzilen® for specific subgroups. In the pre-specified subgroup of patients suffering from tinnitus following otitis media, treatment with Keyzilen® resulted in a reduction of 14.76 points in the TFI from baseline, as compared to 6.19 points for placebo (p-value of 0.048). In active-treated patients who suffered at baseline from severe or extreme tinnitus (a subgroup independent of tinnitus etiology that was not pre-specified), as determined by the Patient Global Impression of Severity, a 15.53 point reduction was observed, as compared to 11.48 points for placebo (p-value of 0.238).

Based on the outcomes from the TACTT2 trial, we amended our protocol for the TACTT3 Phase 3 clinical trial of Keyzilen® in two steps. Under the final, amended trial protocol, the change in TFI score was elevated from a key secondary endpoint to a primary efficacy endpoint, the trial size was increased to enhance statistical sensitivity to the effects of treatment, and the subgroup of patients with otitis media-related tinnitus was included in confirmatory statistical testing along with the overall study population. The change in tinnitus loudness was downgraded from a primary to a secondary efficacy endpoint. As in TACTT2, tinnitus loudness was initially rated on a daily basis; however, the rating frequency was subsequently reduced in between study visits in order to lighten the burden of patients and reduce the potential impact of the frequent measures. Enrollment into the TACTT3 trial was resumed in early 2017 and completed in September 2017.

On March 13, 2018, we announced that preliminary top-line data from the TACTT3 trial indicated that the study did not meet its primary efficacy endpoint of a statistically significant improvement in the Tinnitus Functional Score from baseline to Day 84 in the active treated group compared to placebo either in the overall population or in the otitis media subpopulation. This outcome was confirmed by further analyses. We consider that additional studies with Keyzilen® will be necessary to move the program forward, and that the way how outcomes are measured Keyzilen® will need to be improved in order to provide more robust efficacy data. We intend to fund further development of Keyzilen® either through partnerships or research grants.

Sonsuvi® (AM-111) in Hearing Loss

Sonsuvi® is being developed for the treatment of ASNHL. In sensorineural hearing loss, there is damage to the sensory cells of the inner ear or the auditory nerve. Sensorineural hearing loss is also called “inner ear hearing loss”. Hearing loss is a heterogeneous disorder of many forms with a variety of causes. ASNHL may be triggered by a variety of insults, such as exposure to excessively loud sound, infection, inflammation or certain ototoxic drugs. These insults may also result in tinnitus. According to an article by Alexander and Harris published in Otology & Neurotology in 2013, the average annual incidence of sudden deafness is 66,954 new cases among the U.S. insured population. There are no currently approved treatments for this patient population.

Sonsuvi® contains a synthetic D-form peptide (Brimapitide or D-JNKI-1) that protects sensorineural structures in the inner ear from stress-induced damage. Sonsuvi® has been granted orphan drug status by both EMA and FDA and has been granted fast track designation by the FDA for the treatment of sudden sensorineural hearing loss.

Hearing Loss

Hearing loss, like tinnitus, is a heterogeneous disorder of many forms with diverse etiology. There are two general categories: conductive hearing loss in which sound waves are not conducted efficiently to the inner ear due to build-up of earwax, fluid, or a punctured eardrum; and sensorineural hearing loss, in which there is damage to the inner ear or the auditory nerve. Acute hearing loss can occur in either category. Hearing loss is amenable to pharmaceutical intervention (and thus relevant to our drug development) only when it is sensorineural in origin. ASNHL is often accompanied by tinnitus.

There are two main types of acute hearing loss: hearing loss induced by trauma, such as from a loud rock concert or an explosion; and hearing loss that arises from unknown origins, that is, idiopathically, based on causes suspected to include changes in blood flow to the inner ear, bacterial and viral infections, autoimmune disease and others. The former is known as AAT. The latter is known as ISSNHL. Together they can be defined as ASNHL. In both cases, the onset is sudden. And in both cases, part of the initial hearing loss tends to recover naturally in the days and weeks following the loss; however, some of the loss may remain and, over time, become chronic in nature and less amenable to therapeutic intervention.

ASNHL differs from age-related hearing loss or hearing loss driven by chronic exposure to noise. Those types of hearing loss arise more slowly or on the basis of repeated insults, in slow motion. By contrast, in the case of ASNHL, the effects are felt immediately. This difference in the speed of progression is significant since sudden hearing losses are noticed much more readily.

ASNHL involves a variety of pathologic processes such as massive release of free reactive oxygen species, excessive and pathological stimulation of receptors on neurons by neurotransmitters like glutamate, and inflammation. These reactions, in turn, can damage sensorineural structures of the inner ear such as the sensitive inner and outer hair cells and nerve cells that line the interior of the cochlea. If the stress incident is severe enough, it may lead to permanent cochlear injury with irreversible loss of hair cells and nerve cells. Cell death occurs primarily through so-called programmed cell death, which is driven by damaged cells (apoptosis), and to a lesser extent also through necrosis, which is a passive consequence of gross injury to the cell.

JNK is a signal transmitting enzyme that is stress-activated and regulates a number of important cellular activities. Stresses to the cochlea such as those described above, if severe enough, can activate the JNK signal transduction pathway, leading to the activation of transcription factors such as c-jun and c-fos that are found in the cell nucleus. This activation, in turn, activates genes encoding inflammatory molecules or promoting cell death.

Current Therapies and Unmet Need

Sensorineural hearing loss may have a serious impact on people's personal and professional lives. Severe to profound hearing loss can result in high societal costs, mostly due to reduced work productivity, as reported in 2000 in the International Journal of Technology Assessment in Healthcare. Yet no treatment currently exists that has unequivocal evidence of efficacy for AAT or ISSNHL. There is no FDA- or EMA-approved drug on the market for sensorineural hearing loss. The only remaining therapeutic option is a hearing aid or, in cases of deafness or near-deafness, a cochlear implant.

A patient with the acute form of hearing loss may recover on his or her own, especially if the loss is of low or moderate intensity and severity. This is due to intrinsic repair mechanisms inside the cochlea. However, in other cases the patient may recover only partially or not at all. In those cases, in the absence of effective treatment, acute hearing loss will become chronic and irreversible. There is currently no possibility to regrow or replace sensory structures inside the inner ear that are not recovered in the weeks immediately following the loss.

For ASNHL, non-specific treatments are frequently prescribed, mostly on an off-label empirical basis. These may include glucocorticoids and steroids such as prednisolone or dexamethasone; vasodilators such as pentoxyfilline; rheologics; ionotropics and local anesthetics; antioxidants and thrombolytics.

In the United States, most frequently oral prednisolone is administered for the treatment of ASNHL. Corticosteroids are intended to reduce inflammation and swelling in the ear that may be related to hearing loss. The U.S. treatment guideline issued in 2012 by the American Academy of Otolaryngology/Head & Neck Surgery for ISSNHL lists oral steroids and hyperbaric oxygen as treatment options, but refrains from recommending them in light of the low evidence level for their efficacy. Indeed, Nosrati-Zarenoe and Hultcrantz presented in 2012 in the journal Otology and Neurotology the results of a Swedish placebo controlled trial with oral prednisolone in the treatment of ISSNHL that showed no therapeutic effect on hearing loss from active treatment.

Our Solution — Sonsuvi® (AM-111)

We are developing Sonsuvi® as a treatment for acute inner ear hearing loss. Sonsuvi® contains a synthetic D-form peptide (D-JNKI-1) that acts as a c-Jun N-terminal Kinase (JNK) ligand, thereby protecting sensorineural structures in the inner ear from stress-induced damage. We are developing D-JNKI-1 under a worldwide exclusive license for the treatment of ear disorders from Xigen (Switzerland). Like Keyzilen®, Sonsuvi® is delivered in a biocompatible gel formulation via intratympanic injection. We have established the safety and preliminary efficacy of Sonsuvi® in a Phase 2 and in a Phase 3 clinical trial. The acute stage of hearing loss represents a window in time in which the inner ear can be protected from permanent hearing loss. Sonsuvi® received orphan drug designation by both EMA and FDA in 2005 and 2006, respectively, and was granted fast track designation by the FDA in 2017.

Therapeutic rationale for Sonsuvi® in hearing loss

The proprietary API of Sonsuvi® is brimapitide (D-JNKI-1), a 31 amino acid synthetic D-form peptide that binds to JNK and inhibits activation of transcription factors such as c-jun and c-fos, thereby protecting sensorineural structures from stress-induced inflammation and apoptosis. Brimapitide comprises an active transporter sequence, or D-TAT, that enables Sonsuvi® to cross the round window membrane quickly, diffuse widely throughout the cochlea, transfect sensorineural cells effectively and reach its target inside the cell nucleus. The D-form of the peptide provides for protease resistance and hence enhanced stability. Sonsuvi® was shown to remain pharmacologically active for several days inside the cochlea. The D-form is necessary for Sonsuvi® to cross the RWM.

By attenuating inflammation and protecting cells from apoptosis, we believe that Sonsuvi® reinforces natural recovery processes and helps to prevent or minimize permanent damage respectively chronic hearing loss. Sonsuvi®'s otoprotective effect has been demonstrated in various animal models of cochlear stress, including AAT, acute labyrinthitis (inflammation), drug ototoxicity (aminoglycosides), bacterial infection, cochlear ischemia and cochlear implantation trauma.

We conducted our pre-clinical development program for Sonsuvi® in close collaboration with academic partners and various CROs. Brimapitide was invented by Xigen in Lausanne, Switzerland. In 2003, we signed a Collaboration and License Agreement with Xigen, under which we in-licensed worldwide exclusive rights for use of D-JNKI-1 in the treatment of ear disorders. Under the agreement with Xigen, we have exchanged various pre-clinical and clinical data.

Hearing loss endpoints

Unlike tinnitus, where measures of therapeutic outcomes have to rely on PROs, the evaluation of hearing is based on psychoacoustic measures performed by audiologists. Audiometric procedures and equipment are highly standardized around the world; hearing thresholds are typically determined by presenting pure tones in the 250 Hz to 8 kHz range through headphones or ear inserts (air conduction) or through a vibrator placed behind the ear or on the forehead (bone conduction). An increase in volume of 10 dB is perceived as twice as loud. In other words, a person whose hearing thresholds improved by 10 dB can hear sounds at half the intensity level that was necessary before. A change of this magnitude is generally considered to be clinically relevant. In addition to pure tone audiometry usually speech audiometry is conducted, in which the audiologist measures a patient's ability to hear and correctly understand a series of monosyllabic words.

Sonsuvi® Clinical Development

We have completed three clinical trials of Sonsuvi® that demonstrated its favorable safety profile and efficacy in treating more severe types of ASNHL. We have benefited several times from engaging in a protocol assistance procedure with the EMA and exchanges with the FDA. The design of our pivotal Phase 3 clinical trials was based on the outcomes from our Phase 2 clinical trial and our discussions with the EMA and FDA.

Phase 1/2 Clinical Trial

A Phase 1/2 clinical trial was conducted at two centers in Germany in January 2006, with 11 patients suffering from AAT due to New Year's firecracker accidents. Patients had at least 30 dB hearing loss by pure tone audiometry (average of 4 and 6 kHz) and were treated within 24 hours of onset.

Trial participants received a single dose of Sonsuvi® at either 0.4 mg/mL or 2 mg/mL in a biocompatible gel formulation by intratympanic injection into the most affected ear. The primary endpoint of the trial was the recovery of hearing thresholds from baseline to Day 30. Sonsuvi® was well tolerated by all trial participants, regardless of the dose. The Phase 1/2 trial provided the first indications of therapeutic benefit of Sonsuvi® in humans.

Phase 2 Clinical Trial

To further evaluate the efficacy and safety of Sonsuvi® we conducted a Phase 2b clinical trial between March 2009 and 2012. Since pre-clinical tests had demonstrated Sonsuvi®'s otoprotective effects in many different types of cochlear stress, the patient population was expanded from AAT cases to also include patients affected by ISSNHL. In addition, based on observations from our Phase 1 clinical trial, we expanded the allowed time window from 24 to 48 hours from onset. The design for this Phase 2b trial was discussed with the EMA under a protocol assistance procedure.

As described by Suckfuell and colleagues in an article in Otology & Neurotology in 2014, the trial enrolled 210 participants who suffered from ASNHL (unilateral ISSNHL, uni-or bilateral AAT) with hearing loss of at least 30 dB at the average of the three worst affected frequencies (pure tone average; PTA) and onset not more than 48 hours previously. Sonsuvi® was dosed at 0 mg/mL (placebo), 0.4 mg/mL (Low Dose) and 2.0 mg/mL (High Dose). All patients without a clinically relevant hearing recovery on Day 7 were given the option to take a course of oral prednisolone as a reserve therapy. The primary efficacy endpoint was hearing loss recovery from baseline to Day 7 at the three worst affected frequencies. The trial consisted of a baseline assessment and four follow-up visits on Days 3, 7, 30, and 90.

Sonsuvi® demonstrated a favorable safety profile in this trial. There were no statistically significant differences in the occurrence of clinically relevant hearing deterioration in the treated ear. Also, there were no apparent differences in the frequency of adverse events between placebo and Sonsuvi® treated patients at any time points, no systemic side effects and no negative impact on balance or tinnitus. There were transient procedure related effects such as ear discomfort or pain, incision site complications or middle ear infection in less than 5% of cases.

Overall, the trial did not meet its primary efficacy endpoint. Analysis of PTA improvement by hearing loss severity in accordance with a commonly used hearing loss classification revealed unexpectedly strong spontaneous recovery for lesser severities: by Day 7, placebo-treated patients enrolling with mild-to-moderate hearing loss (PTA < 60 dB) had recovered more than three quarters of their initial loss, whereas for patients with severe to profound hearing loss (PTA ≥ 60 dB), it was only about one quarter. Post-hoc analyses in the severe-to-profound hearing loss subgroup demonstrated superiority of Sonsuvi® 0.4 mg/mL over placebo for the primary endpoint, improvement in absolute PTA, as well as for co-primary efficacy endpoints, hearing improvement relative to the initial hearing loss and frequency of complete hearing recovery. Further, the improvement in word recognition scores was nominally significant as well as the frequency of complete tinnitus remission.

The Sonsuvi® 2.0 mg/mL group overall showed improvement between the Sonsuvi® 0.4 mg/mL and the placebo groups, without reaching statistical significance. However, differences between the two active treatment groups were nominally not significant.

Phase 3 Clinical Program

Based on Phase 2 clinical trial outcomes, we prepared and initiated a Phase 3 clinical program including confirmatory testing of Sonsuvi® 0.4 mg/mL as well as exploring potential incremental therapeutic benefits from a higher concentration (0.8 mg/mL) in ISSNHL patients. Since a "bell shaped" dose response curve was observed in animal studies, testing a concentration between 0.4 and 2.0 mg/mL was expected to shed further light on the dose effect relationship in humans. In view of the high spontaneous recovery in the mild to moderate hearing loss subgroup observed in Phase 2, recruitment was limited to patients experiencing severe or profound ISSNHL, i.e. patients with more pronounced medical need. Further, the time window for inclusion was extended from up to 48 hours to up to 72 hours from ISSNHL onset as the magnitude of the therapeutic effect in Phase 2 did not appear to decrease the later treatment was started. This enlargement also aligned the duration of the time window with the period over which ISSNHL can develop, which is defined, e.g. by the U.S. practice guideline for sudden sensorineural hearing loss, as 72 hours.

The first Phase 3 trial, called HEALOS, started enrollment in November 2015. The trial enrolled a total of 256 patients in several European and Asian countries. On November 28, 2017, we announced that the HEALOS Phase 3 clinical trial that investigated Sonsuvi® in the treatment of acute inner ear hearing loss did not meet the primary efficacy endpoint of a statistically significant improvement in hearing from baseline to Day 28 compared to placebo for either active treatment groups in the overall study population. However, a post-hoc analysis of the subpopulation with profound acute hearing loss (PTA ≥ 90 dB at baseline in accordance with a commonly used classification of hearing loss severity) revealed a clinically meaningful and nominally significant improvement in the Sonsuvi® 0.4 mg/mL treatment group. Further, patients treated with Sonsuvi® 0.4 mg/mL showed a nominally significantly lower incidence of no hearing improvement compared to placebo by Day 91 as well as a superior improvement in word recognition score. Outcomes with Sonsuvi® 0.8 mg/mL tended to be somewhat less pronounced than those observed for Sonsuvi® 0.4 mg/mL. Sonsuvi® was well tolerated and the primary safety endpoint was met.

Together with the outcomes of the HEALOS trial, we announced that ASSENT, the second Phase 3 clinical trial investigating Sonsuvi®, was terminated early in order to avoid the need for substantial protocol changes and interruptions of enrollment pending feedback from health authorities on the regulatory pathway. ASSENT was planned to enroll a total of 300 patients in the US, Canada and South Korea. In contrast to HEALOS and the Phase 2 trial, where patients with insufficient hearing recovery had the option of receiving a course of oral corticosteroids as reserve therapy, all patients in ASSENT would receive oral corticosteroids as a background therapy. At the time of early termination, the ASSENT trial had recruited 56 patients.

Based on the HEALOS results, we submitted the design of a new pivotal trial with AM-111 0.4 mg/mL in patients suffering from acute profound hearing loss to the EMA and subsequently also to the FDA for review. Through a Protocol Assistance procedure the EMA endorsed the proposed trial design, choice of efficacy and safety endpoints, as well as the statistical methodology. In a Type C meeting with written responses, the proposed choice of primary and secondary efficacy endpoints, the safety endpoints, as well as the planned sample size and statistical methodology were also endorsed by the FDA. Following this feedback, we have mandated a transaction advisory firm to identify potential partners for the Sonsuvi® development program and provide support for partnering discussions and negotiations. If successful, this may result in one or several sale, out-licensing or co-development transaction(s) on a global or regional scale.

AM-125 in Vestibular Disorders

Vestibular Disorders

Balance disorders are medical conditions that evoke the sensation of unsteadiness, dizziness or vertigo. Patients suffering from balance disorders are often profoundly impacted in their daily activities. According to the NIDCD, more than four out of 10 Americans, at some point in their lives, experience an episode of dizziness significant enough to see a doctor. According to research by Saber Tehrani and colleagues published in the journal Academic Emergency Medicine in 2013 there are almost 4 million emergency room visits per year in the U.S. for problems of dizziness or vertigo. Balance problems can be caused by many different health conditions, medications or anything that affects certain areas of the brain or the inner ear labyrinth. Balance disorders originating from the inner ear labyrinth include benign paroxysmal positional vertigo, or positional vertigo, labyrinthitis, vestibular neuronitis and Meniere's disease, a chronic condition characterized by severe episodic vertigo, tinnitus, and fluctuating hearing loss.

In case of vertigo, patients experience a false sensation of movement of oneself or the environment. This can be a spinning or wheeling sensation, or they simply feel pulled to one side. This may lead to imbalance, nausea or vomiting. The cause of vertigo can be an imbalance between the left and right vestibular systems in signaling position and acceleration to the brain. The symptom of vertigo may partially or fully resolve thanks to spontaneous recovery of the peripheral vestibular function and/or through compensation of the imbalance at the brain level, which is known as vestibular compensation.

The imbalance between the left and right vestibular systems and thus the sensation of vertigo may be reduced by dampening the vestibular function in the unaffected, opposite inner ear through pharmacotherapy. This minimizes the extent of the imbalance falsely interpreted as movement. Most existing therapies rely on this strategy to minimize vertigo symptoms, but also have unintended sedative effects. Examples include meclizine, benzodiazepines, dimenhydrinate or amitriptyline.

Betahistine is widely used around the world for the treatment of vestibular disorders, notably Meniere's disease and vertigo. Its development goes back to the use of intravenous histamine, which provided symptomatic relief for these disorders. Betahistine is a structural analog of histamine. It acts as a partial histamine H1-receptor agonist and, more powerfully, as a histamine H3-receptor antagonist. Betahistine has been shown to increase cochlear, vestibular and cerebral blood flow, facilitate vestibular compensation and inhibit neuronal firing in the vestibular nuclei. Unlike other drugs, it has no sedating effect. Betahistine is typically taken orally with a recommended daily dose of 24 to 48 mg, divided in 2 or 3 single doses.

Betahistine is generally recognized as a safe drug and there exists a large body of data on the pharmacology, pharmacokinetics and toxicology of the compound. It is approved in about 115 countries world-wide for the treatment of Meniere's disease and vestibular vertigo, but not in the United States. In 1970, the Commissioner of FDA withdrew approval of the NDA after the discovery that the submission contained unsubstantiated information about some patients in the efficacy studies upon which approval was based. Today, betahistine is available in the United States only from compounding pharmacies or through importation. Despite limited availability, a survey by Clyde and colleagues published in Otology & Neurotology in 2017 revealed that 56% of U.S. neurotologists and 16% of generalists use betahistine and 20 – 30% of neurotologists use it often or always when treating patients with Meniere's disease.

Various studies and meta-analyses have demonstrated therapeutic benefits of betahistine in both the treatment of vertigo as well as in supporting vestibular rehabilitation. However, the evidence for therapeutic benefits is variable, and it has been suggested that efficacy could be increased with higher doses and/or longer treatment periods. It is well known that orally administered betahistine is rapidly and almost completely metabolized into 2-pyridylacetic acid, also known as 2-PAA, which lacks pharmacological activity. As a consequence the bioavailability of oral betahistine is estimated to be very low.

Our Solution — AM-125

On February 2, 2017, we entered into an asset purchase agreement with Otifex, pursuant to which we have purchased various assets related to betahistine dihydrochloride in a spray formulation, which we intend to develop for intranasal treatment of vertigo under the name AM-125.

The assets include data from a randomized placebo controlled dose escalating Phase 1 clinical trial in 40 healthy volunteers. The trial demonstrated good tolerability of intranasal betahistine and significantly higher betahistine concentrations in blood plasma than reported for oral betahistine administration. Comparing the betahistine concentrations in plasma with those from an independent Phase 1 clinical trial with oral betahistine showed a relative bioavailability (dose adjusted) for intranasal administration that was 20 – 40 times higher than with oral administration. In 2018, we conducted a second Phase 1 clinical trial with AM-125 in healthy volunteers. The trial showed superior bioavailability (unadjusted) over a range of four intranasal betahistine doses compared to oral betahistine observed, with plasma exposure being 6 to 29 times higher (p-value between 0.056 and $p < 0.0001$). Further, it confirmed the good safety profile of intranasal betahistine and showed that the treatment was well tolerated when administered three times daily for three days.

We have discussed the regulatory requirements for AM-125 during a Pre-IND meeting with the FDA and in the context of scientific advice meetings with the EMA and two European national health authorities to further define the development program. We believe that, if approved, AM-125 could become the first betahistine product for the treatment of vertigo in the United States.

In 2019, we plan to initiate a randomized placebo-controlled Phase 2 clinical study with AM-125 in the first quarter. The "TRAVERS" Phase 2 trial will enroll 138 patients suffering from acute vertigo following surgical removal of a vestibular schwannoma, a tumor growing behind the inner ear. It will be conducted in several European countries and potentially, Canada. The TRAVERS trial will have two parts: In Part A, five ascending doses of AM-125 or placebo, administered three times daily over a total of four weeks, will be tested in a total of 50 patients. In addition, oral betahistine 48 mg will be tested in 16 patients under open-label conditions for reference. Based on an interim analysis, two doses will be selected and tested in an estimated 72 patients in Part B.

AM-201 in Antipsychotic-Induced Weight Gain

Antipsychotic-induced weight gain

The use of second generation antipsychotic drugs such as olanzapine or clozapine can be associated with severe side effects such as weight gain, metabolic dysregulation and somnolence. These side effects not only have a negative effect on patients' compliance with medication, but expose them to additional hazards: weight gain is strongly correlated with metabolic dysregulation leading to diabetes and cardiovascular disease; and somnolence may severely impact quality of life, affecting learning, social interactions or tasks such as driving or operating machinery. These adverse events are mainly attributed to the histamine H1 receptor antagonistic properties of these agents. Treatment with these antipsychotic drugs reduces the activity of the H1 receptor, which in turn causes increased eating and weight gain.

According to the U.S. prescription information for olanzapine, accumulated evidence shows that patients gain on average 2.6 kg over a treatment duration of 6 weeks. During long-term treatment (≥ 48 weeks) patients gain on average 5.6 kg as shown in a review published by Citrome and colleagues published in the journal Clinical Drug Investigations in 2011. Over that time period, 64%, 32%, and 12% of patients treated with olanzapine gain at least 7%, 15%, or 25% of their baseline body weight, respectively.

The concerns about antipsychotic-induced weight gain and consequent metabolic changes have led the FDA to highlight these risks as warnings in the prescribing information of certain antipsychotics and call for regular monitoring of glycemic control, lipid profile and weight. These concerns are also reflected in treatment guidelines, which do not recommend olanzapine or clozapine as first-line treatments, despite the fact that meta-analyses such as one by Leucht and colleagues published in 2013 in the journal Lancet show that they are among the most effective treatments for schizophrenia.

Our Solution — AM-201

On May 15, 2018, we announced the expansion of our intranasal betahistine development program beyond the treatment of vertigo into mental health supportive care indications. Under project code AM-201 we intend to develop intranasal betahistine for the prevention of antipsychotic-induced weight gain. Betahistine is thought to counteract the effects of antipsychotics such as olanzapine and to relieve the inhibitory effect on the H1 receptor by binding to and activating the H1 receptor to normalize/reduce the food take and consequently lead to reduced weight gain. We believe the weight-attenuating effect is intensified by betahistine's property as antagonist at the H3 receptor. We have discussed our development plan for AM-201 with the FDA during a Pre-IND meeting. In its written response, the FDA supported the planned conduct of a multiple dose Phase 1 trial with AM-201 administered to healthy subjects in combination with olanzapine to evaluate the pharmacokinetics, pharmacodynamics, and safety, and to establish proof-of-concept. Further, the FDA endorsed weight gain normalized to baseline body weight versus placebo as reasonable primary efficacy endpoint for a subsequent Phase 2 trial.

We expect to initiate the Phase 1b proof-of-concept trial with AM-201 in the first quarter of 2019. The randomized double blind placebo controlled trial will be conducted in a European country and enroll 50 healthy volunteers who will receive either AM-201 or placebo concomitantly with olanzapine over four weeks. Doses will be escalated in five steps. We expect to conclude the study and obtain results during 2019.

Competition

We may face competition from different sources with respect to our product candidates Keyzilen® (AM-101), Sonsuvi® (AM-111), AM-125 and AM-201 and our other pipeline products or any product candidates that we may seek to develop or commercialize in the future. Because there are a variety of means to block the activity of NMDA receptors or the JNK pathway, our patents and other proprietary protections for Keyzilen® and Sonsuvi® may not prevent development or commercialization of all viable product candidates that are different from our lead product candidates.

Any product candidates that we successfully develop and commercialize will compete with existing therapies, even if they are not licensed specifically for use in our target therapeutic indications or if they lack clear proof of efficacy.

There exist no FDA or EMA approved products for the treatment of acute inner ear tinnitus or acute inner ear hearing loss; however, some drug products such as pentoxifylline, gingko biloba, corticosteroids, betahistine, trimetazidine or piracetam are frequently prescribed off-label. Some of them are even licensed as tinnitus or hearing loss treatments in certain countries of the European Union. A variety of drug products that are licensed or used off-label for the treatment of vestibular disorders and Meniere's disease exist, including steroids, diuretics, anti-emetics or anti-nausea medications. In many countries outside the United States, oral betahistine is the standard of care and licensed for the treatment of Meniere's disease and vestibular vertigo.

Possible competitors may be biotechnology and pharmaceutical companies as well as academic institutions, government agencies and private and public research institutions, which may in the future develop products to treat acute inner ear tinnitus or hearing loss or vertigo. Any product candidates that we successfully develop and commercialize will compete with new therapies that may become available in the future. We believe that the key competitive factors affecting the success of our product candidates, if approved, are likely to be efficacy, safety, convenience, price, tolerability and the availability of reimbursement from government and other third-party payors.

Acute inner ear tinnitus

There are a number of products in pre-clinical research and clinical development by third parties to treat tinnitus in the broader sense. Most of them are aiming to provide symptomatic relief (without treating the underlying cause) and targeting chronic rather than acute tinnitus. Examples include TRT or tinnitus maskers as well as more recent approaches like transcranial magnetic stimulation, vagus nerve stimulation, or customized sound therapy. Based on publicly available information, we have further identified the following drug product candidates that are currently in clinical development:

- Autifony Therapeutics Ltd. has a Kv3 potassium channel agonist product candidate (AUT00063) that is designed for oral administration. In 2014 Autifony initiated a Phase 2 study with AUT00063 in patients with post-acute tinnitus. Following an interim analysis, Autifony announced in October 2015 that it would halt enrollment in its Phase 2 trial due to a lack of efficacy.
- Otonomy Inc. acquired an early stage NMDA receptor antagonist product candidate (NST-001, gacyclidine) from Neurosystec Inc. in October 2013. According to public information, Otonomy intends to develop a polymer-based formulation of gacyclidine for the treatment of tinnitus that will provide a full course of treatment from a single intratympanic injection. OTO-311 has been evaluated in a Phase 1 trial. Following a change in formulation, Otonomy is planning to initiate a Phase 1/2 trial with the modified drug product OTO-313 in 2019.

Based on publicly available information, OTO-313 will target a similar group of tinnitus patients. Its competitive strength will ultimately depend on the demonstration of clinical efficacy and safety and its comparison with Keyzilen®. Progress in the development of Keyzilen® and in particular market approval may attract increased interest in developing treatments for acute inner ear tinnitus and may lead to the arrival of new competitors.

Acute inner ear hearing loss

There are a number of product candidates in pre-clinical research and clinical development by third parties that aim to prevent or treat acute inner ear hearing loss. Based on publicly available information, we have identified the following drug product candidates that are currently in clinical development:

- Autifony Therapeutics Ltd. has a Kv3 potassium channel agonist product candidate (AUT00063) that is designed for oral administration. Autifony conducted a Phase 2 trial with AUT00063 in the treatment of speech-in-noise deficits in elderly patients. Autifony announced in August 2016 that the study showed no treatment benefit for AUT00063. In July 2016, the company announced a pilot trial with AUT00063 in adult cochlear implant users in the United Kingdom.
- GenVec, Inc. is developing CGF166, E1-, E3-, E4-deleted human adenovector serotype 5 (Ad5) backbone in collaboration with Novartis and has initiated a Phase 1/2 study for the treatment of hearing loss and vestibular dysfunction. The first patient was treated in October 2014.

- Nordmark, a German company, is developing Ancrod, the biologically active substance from the venom of the Malayan Pit Viper (Calloselasma rhodostoma), for the treatment of sudden sensorineural hearing loss and has initiated a Phase 2 program.
- Sound Pharma has a product candidate (SPI-1005, ebselen), that mimics and prompts production of the enzyme glutathione peroxidase and is designed for oral administration. In a Phase 2 clinical trial SP-1005 was tested for the prevention of noise-induced hearing loss in young adults. The study showed a reduction in the temporary hearing threshold that in one dose was better by 2.75 dB than in the placebo group.
- Otologic Pharmaceutics, Inc. has a product candidate (HPN-07) designed for treatment of acute hearing loss by way of oral administration. A Phase 1 trial was completed in December 2015. A Phase 2 clinical trial is under preparation.
- Sensorion, a French company, is developing SENS-401 (R-azasetron besylate) for the treatment of sudden sensorineural hearing loss by way of oral administration. The company plans to initiate a Phase 2 trial in 2019. Sensorion has received orphan drug designation by the EMA for sudden sensorineural hearing loss.
- Southern Illinois University has an antioxidant product candidate (D-methionine) that is designed for oral administration in the prevention and treatment of noise induced hearing loss and currently being tested in a late stage study with the Department of Defense.
- Strekin AG, a privately held Swiss company, has an agonist of the peroxisome proliferator (STR001) that it plans to develop for surgery induced haring loss. A Phase 2 trial was initiated in 2016. Strekin has received orphan drug designation by the EMA for sudden sensorineural hearing loss.

We believe that Sonsuvi® is the only product candidate administered after an incidence of acute hearing loss that so far has demonstrated in a randomized, placebo controlled clinical trial a clinically relevant and significant improvement in hearing. To our knowledge, we are also the only company to have obtained orphan drug designation for a product candidate in the treatment of ASNHL in the United States. To the extent that other drug developers demonstrate clinical efficacy for their product candidates in the prevention and treatment of permanent hearing loss from ASNHL, our competitive position may be weakened, and the market exclusivity under the orphan drug designation may be circumvented.

Vestibular Disorders

There are a number of product candidates in clinical development by third parties that aim to prevent or treat vertigo. Based on publicly available information, we have identified the following drug product candidates that are currently in clinical development:

- Otonomy is developing a polymer-based formulation for the steroid dexamethasone (Otividex; OTO-104) for patients with Meniere's disease. In August 2017 Otonomy announced that a Phase 3 clinical trial conducted in the United States had failed to show a treatment effect of OTO-104 against placebo and that a European Phase 3 clinical trial was terminated early. In November 2017 the company announced that the European study showed a statistically significant reduction in the count of definitive vertigo days.
- Sensorion is developing SENS-111, a histamine H_4 receptor antagonist, for the oral treatment of acute vertigo crises. A Phase 2 trial started enrolling patients with acute unilateral vestibulopathy in 2017. Results are expected in the second half of 2019.
- Sound Pharma has a product candidate (SPI-1005, ebselen), that mimics and prompts production of the enzyme glutathione peroxidase and is designed for oral administration. In October 2017 Sound Pharmaceuticals announced a Phase 2 clinical trial with SP-1005 to treat patients with Meniere's disease.

The aforementioned developments have the potential to compete with AM-125. Likewise, AM-125, if approved, will compete with products that are licensed or used off-label for the treatment of vestibular disorders and Meniere's disease, including steroids, diuretics, anti-emetics or anti-nausea medications as

well as oral betahistine, the standard of care for treatment of Meniere's disease and vestibular vertigo outside the United States. Although we expect that AM-125 will offer benefits over oral betahistine due to the ability to bypass the strong first-pass metabolism associated with oral intake and provide for a higher bioavailability and avoid gastric side effects, it may take time to change prescribing and usage patterns in favor of the newer product.

Antipsychotic-induced weight gain

There are a number of product candidates in clinical development by third parties that aim to prevent or treat antipsychotic-induced weight gain. Based on publicly available information, we have identified the following drug product candidates that are currently in clinical development:

- ALKS-3831 is a fixed-dose combination of olanzapine and samidorphan, a novel opioid system modulator, which is being developed by Alkermes Inc. with the specific aim of providing the therapeutic benefits of olanzapine with less weight gain than olanzapine monotherapy. On November 29, 2018 Alkermes announced that the ENLIGHTEN-2 phase 3 trial with ALKS-3831 had met its coprimary endpoints of mean % body weight change from baseline and % of patients with ≥10% weight gain. The reported reduction in weight gain over 6 months was 37% versus olanzapine monotherapy. and that the company expects to file for an NDA in mid-2019.

If approved, ALKS-3831 will reach the market well before AM-201. We believe that our product may provide various benefits over ALKS-3831, notably that it does not come in a fixed dose combination, allowing for dosing flexibility, and that it may be used with other antipsychotic drugs than olanzapine.

As weight gain is associated with immediate metabolic side effects it is advisable to prevent antipsychotic-induced weight gain rather than seek to treat the overweight once it has developed. Weight monitoring, dietary and lifestyle changes as well as behavioral and cognitive counseling present the most effective non-pharmacologic ways to prevent and also treat antipsychotic weight gain. Pharmacologic approaches include the switch to an alternative antipsychotic treatment strategy, which however can be associated with a loss of efficacy or the appearance of other side effects. Limited evidence for efficacy with metformin as an exploratory adjuvant to prevent antipsychotic-induced weight gain has been demonstrated.

Intellectual Property

Patents

We seek regulatory approval for our products in disease areas with high unmet medical need, great market potential and where we have a proprietary position through patents covering various aspects of our products, e.g., composition, dosage, formulation, and use, etc. Our success depends on an intellectual property portfolio that supports our future revenue streams as well as erects barriers to our competitors. For example, we have broad disclosures in our patent applications and can pursue patent claims directed to our own leading product candidates as well as claims directed to certain potentially competing products. In addition, our earlier filed patent applications are prior art to others including certain of our competitors who filed their patent applications later than ours. We are maintaining and building our patent portfolio through: filing new patent applications; prosecuting existing applications and licensing and acquiring new patents and patent applications.

Despite these measures, any of our intellectual property and proprietary rights could be challenged, invalidated, circumvented, infringed or misappropriated, or such intellectual property and proprietary rights may not be sufficient to permit us to take advantage of current market trends or otherwise to provide competitive advantages.

As of December 31, 2018, we own five issued U.S. patents and five pending U.S. patent applications along with foreign counterparts of particular patents and applications in various jurisdictions. We co-own four of our issued U.S. patents, and one of our pending patent applications with INSERM, along with their foreign counterparts, pursuant to the terms of our co-ownership and exploitation agreement. In addition, we co-own one of our pending applications with Xigen pursuant to the terms of our collaboration and license agreement.

In addition, as of December 31, 2018, we have exclusively licensed from Xigen eleven issued U.S. patents and two pending U.S. patent applications, along with their foreign counterparts in various jurisdictions that cover the composition of matter or method of use of JNK ligand peptides in a limited field including the intratympanic treatment of ASNHL.

With respect to our issued patents in the United States, we may also be entitled to obtain a patent term extension to extend the patent expiration date. For example, in the United States, we can apply for a patent term extension of up to 5 years for one of the patents covering a product once the product is approved by the FDA. The exact duration of the extension depends on the time we spend in clinical trials as well as getting a new drug application approval from the FDA.

Keyzilen®

We are the owner or co-owner of patents and patent applications relating to Ketamine or its use in inner ear tinnitus. In particular, we have an agreement entitled "Co-Ownership/Exploitation Agreement" with INSERM with respect to its Ketamine patent portfolio. We have rights to four issued U.S. patents and one pending U.S. applications and corresponding patents and applications in other jurisdictions including Europe, Eurasia, Australia, Canada, Japan, Brazil, China, South Korea, Israel, India, Mexico, Philippines, Russia, South Africa and New Zealand, covering formulation and use of Ketamine. Our issued patents and pending patent applications relating to Keyzilen® are expected to expire between 2024 and 2028, prior to any patent term extensions to which we may be entitled under applicable laws.

Sonsuvi®

We are the exclusive licensee under our agreement with Xigen of a portfolio of patents and patent applications that relate, among other things, to JNK ligand peptides or their use in hearing loss. This portfolio includes twelve issued U.S. patents and three pending U.S. applications along with their foreign counterparts in various jurisdictions including, Europe, Australia, Brazil, Canada, Eurasia, South Korea, Israel, India, Mexico, Ukraine and Japan, that cover the composition of matter or method of use of the JNK ligand peptides. These licensed patents and patent applications relating to Sonsuvi® are expected to expire between 2020 and 2027, prior to any patent term extensions to which we may be entitled under applicable laws. In addition, we co-own two patent families with Xigen related to use of JNK ligand peptides for the treatment of Meniere's disease or tinnitus.

We have several areas of disagreement with Xigen, including (i) our interpretation of the scope of the exclusive worldwide license granted to us by Xigen, (ii) the assignment by Xigen of certain of the patents covered by the license and (iii) Xigen's refusal to grant its consent for the disclosure of certain provisions of our agreement in the prospectus associated with our initial public offering and the filing of a redacted version of the agreement with the SEC. Although the difference in interpretation over the scope of the license has no impact on our current or planned use of Sonsuvi® and we have been assured by Xigen and its assignee that the assignment of patents is without prejudice to our license, these areas of disagreement could adversely affect our relationship with Xigen and our business, commercialization prospects and financial conditions. Although Xigen has not taken any action as of December 31, 2018, any resulting litigation could result in substantial legal expenses and potentially the loss of our right to commercialize Sonsuvi®.

Intranasal Betahistine

We have acquired one patent from Otifex directed to intranasal application of betahistine for Eustachian tube dysfunction that is issued in the United States. In addition, we purchased from Otifex a patent application on the composition and use of intranasal betahistine. Further, we acquired in 2018 two U.S. patents relating to the use of betahistine for the prevention and treatment of olanzapine induced weight gain, and we entered into a binding letter of intent to acquire the right to in-license two U.S. patents relating to the use of betahistine for the treatment of attention deficit/hyperactivity disorder and atypical depression.

Proprietary Rights

In addition to patent protection, we intend to use other means to protect our proprietary rights. We may pursue marketing exclusivity periods that are available under regulatory provisions in certain countries,

including the US, Europe and Japan. For example, if we are the first to obtain market approval of a small molecule product in the United States, we would expect to receive at least 5 years of market exclusivity in the U.S.

Janssen, a subsidiary of Johnson & Johnson, has been testing Esketamine in a spray formulation for intranasal treatment of treatment-resistant depression in several clinical trials to date, and completed a Phase 3 program. In November 2014, the FDA designated Esketamine a 'breakthrough therapy' for this indication. In the event that Janssen receives marketing authorization prior to us receiving marketing authorization for Keyzilen®, we would lose the potential benefit of a five year market exclusivity period that we would otherwise expect to obtain.

Furthermore, orphan drug exclusivity has been or may be sought where available. Such exclusivity has a term of 7 years in the United States and 10 years in Europe. We have obtained orphan drug designation for Sonsuvi® for the treatment of ASNHL in the United States and Europe. Orphan drug protection has been or may be sought where available if such protection also grants 7 years of market exclusivity. In addition, we have acquired a U.S. orphan drug designation for betahistine for the treatment of obesity associated with Prader-Willi syndrome.

We have obtained U.S. trademark registrations for Auris, Auris Medical, Auris Medical Cochlear Therapies (and Design), Keyzilen® and Sonsuvi®. Further, we have obtained several U.S. trademark registrations for betahistine.

In addition, we rely upon unpatented trade secrets, know-how, and continuing technological innovation to develop and maintain our competitive position. We seek to protect our ownership of know-how and trade secrets through an active program of legal mechanism including assignments, confidentiality agreements, material transfer agreements, research collaborations and licenses.

Collaboration and License Agreements

INSERM

In 2006, we entered into a co-ownership/exploitation agreement with the INSERM, a publicly funded government science and technology agency in France. Pursuant to the terms of the agreement, we were granted the exclusive right to exploit any products derived from patents that resulted from our joint research program with INSERM that was conducted in 2003 to 2005 and led to the development of Keyzilen®. Pursuant to the terms of the co-ownership/exploitation agreement, we are given the exclusive right to exploit the patents issuing from the filed patent applications for all claimed applications, including the treatment of tinnitus, in order to develop, promote, manufacture, cause to be manufactured, use, sell and distribute any products, processes or services deriving from such patents, including Keyzilen®, in any country in which these patent applications have been filed during the term of the agreement. We alone are entitled to grant manufacturing or sales licenses for any patents to our subsidiaries and/or third parties. INSERM is entitled to use the inventions covered by the patents and applications for its own research purposes, free of charge, but may not generate any direct or indirect profits from such use. Pursuant to the terms of our agreement with INSERM, we are required to finance research and development work towards achieving certain specified marketing authorizations, and to use best efforts in so far as commercially and financially feasible to develop, market, and obtain regulatory authorization for products covered by such patents.

As consideration for the exclusive rights granted to us under the agreement, we have agreed to pay INSERM a two tiered low single digit royalty (where the higher rate is due on any net sales above a certain threshold) on the net sales of any product covered by the patents (including the use of Keyzilen® in the treatment of tinnitus triggered by cochlear glutamate excitotoxicity) earned in each country in which these patent applications have been filed during the term of the agreement. We have also agreed to pay INSERM a low double digit fee on any sums of any nature (except royalties and certain costs) collected by us in respect of the granting of licenses to third parties.

The agreement will remain in force until the last of the patents covered by the agreement expires or becomes invalid. The patent covered by the agreement with the latest expiration date expires in 2028. The agreement will be terminated if we cease operations or are liquidated, may be terminated by either party in

case of non-performance by the other party and may be terminated by INSERM in the absence of sales of a product deriving from the patents for a period from when it first marketed and if such a product is not marketed for a period from the date when marketing authorization is obtained.

Xigen

In October 2003, we entered into a collaboration and license agreement with Xigen, pursuant to which Xigen granted us an exclusive worldwide license to use specified compounds to develop, manufacture and commercialize "pharmaceutical products as well as drug delivery devices and formulations for local administration of therapeutic substances to the inner ear for the treatment of ear disorders" (the Area). We also have a right of first refusal to license certain additional compounds developed by Xigen which may be used for the Area, specifically any cell permeable inhibitors to effectively block certain signal pathways in apoptotic processes.

Under this agreement, we made an upfront payment to Xigen of CHF 200,000 and we are obligated to make development milestone payments on an indication-by-indication basis of up to CHF 1.5 million and regulatory milestone payments on a product-by-product basis of up to CHF 2.5 million, subject to a mid-twenties percentage reduction for smaller indications, e.g., those qualifying for orphan drug status. To date, we have paid CHF 1.325 million to Xigen under the agreement. We will be required to pay Xigen a mid-single digit percentage royalty on net sales of each licensed product that uses a compound licensed under the agreement, which royalty for a given indication shall be partially offset by milestone payments we have paid for such indication, until the later of 10 years after the first commercial sale of any licensed product using such licensed compound in any country, and the first expiration of a patent owned by or exclusively licensed to Xigen that covers the use of such licensed compound in any country, subject to our obligation to enter into good faith negotiations with Xigen, upon expiration of the relevant patent on a licensed compound, about the conditions of our further use of such licensed compound.

Under this agreement we and Xigen grant each other access to non-clinical or clinical data relating to the compounds licensed under the agreement free of charge for use in the other party's proprietary development programs. We have also agreed, upon Xigen's request, to offer third parties access to our non-clinical and clinical data relating to compounds licensed under the agreement for use outside the field of our license, provided that with respect to third party access, we are compensated for a portion of our costs in obtaining such data. Further, pursuant to our agreement, we and Xigen agreed to enter into a supply agreement within a specified period after the date of the agreement, which period has since passed, pursuant to which Xigen would supply us with licensed compounds. We did not enter into such a supply agreement with Xigen. Xigen supplied us with the API for Sonsuvi® for a period of time, but we presently are receiving our supply from an alternative supplier.

Xigen is responsible for maintaining the patents licensed to us under our agreement. New patents filed by us for specific inner ear indications or formulations of compounds licensed under our agreement are jointly owned by us and Xigen, and exclusively licensed to us in our field. We retain all know-how and other results from our development of compounds licensed under the agreement.

Our agreement with Xigen remains in effect until terminated. Either we or Xigen may terminate the agreement for the other party's material breach or bankruptcy, in the event of force majeure, or after a specified period following the date of the agreement, if we are not progressing any activities with respect to the licensed compound. This period has passed for Sonsuvi®. In October 2013, Xigen assigned certain of the patents relevant to the agreement to Xigen Inflammation Ltd, Cyprus, an unaffiliated party.

There have been several areas of disagreement with Xigen, primarily related to interpreting the definition of the Area, the transfer of patents to Xigen Inflammation Ltd. and to the disclosure of certain provisions of the agreement in the context of our initial public offering.

Manufacturing

We currently rely on and expect to continue to rely on third parties for the supply of raw materials and to manufacture drug supplies for clinical trials of our product candidates, including Keyzilen®, Sonsuvi®, AM-125 and AM-201. For the foreseeable future, we expect to continue to rely on such third parties for the manufacture of any of our product candidates on a clinical or commercial scale, if any of our product

candidates receives regulatory approval. Reliance on third-party providers may expose us to more risk than if we were to manufacture product candidates ourselves. The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA or other regulatory authorities pursuant to inspections that will be conducted after we submit our NDA or comparable marketing application to the FDA or other regulatory authority. We do not have control over a supplier's or manufacturer's compliance with these laws, regulations and applicable cGMP standards and other laws and regulations, such as those related to environmental health and safety matters. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. Any failure to achieve and maintain compliance with these laws, regulations and standards could subject us to the risk that we may have to suspend the manufacturing of our product candidates or that obtained approvals could be revoked, which would adversely affect our business and reputation. Furthermore, third-party providers may breach agreements they have with us because of factors beyond our control. They may also terminate or refuse to renew their agreements because of their own financial difficulties or business priorities, potentially at a time that is costly or otherwise inconvenient for us. If we were unable to find adequate replacement or another acceptable solution in time, our clinical trials could be delayed or our commercial activities could be harmed.

In addition, the fact that we are dependent on our suppliers and other third parties for the manufacture, storage and distribution of our product candidates means that we are subject to the risk that the products may have manufacturing defects that we have limited ability to prevent or control. The sale of products containing such defects could result in recalls or regulatory enforcement action that could adversely affect our business, financial condition and results of operations.

Growth in the costs and expenses of components or raw materials may also adversely influence our business, financial condition and results of operations. Supply sources could be interrupted from time to time and, if interrupted, that supplies could be resumed (whether in part or in whole) within a reasonable timeframe and at an acceptable cost or at all.

Commercialization Strategy

Given our current stage of product development, we currently do not have a commercialization infrastructure. If any of our product candidates is granted marketing approval, we intend to focus our initial commercial efforts in the United States and select European markets, which we believe represent the largest market opportunities for us. In those markets, we expect our commercial operations to include our own specialty sales force that we will specifically develop to target ENTs and specialists in neurotology and neurology, both in hospitals and in private practice. In other markets, we expect to seek partnerships that would maximize our products' commercial potential.

Government Regulation

Product Approval Process

The clinical testing, manufacturing, labeling, storage, distribution, record keeping, advertising, promotion, import, export and marketing, among other things, of our product candidates are subject to extensive regulation by governmental authorities in the United States and other countries. The FDA, under the Federal Food, Drug, and Cosmetic Act, regulates pharmaceutical products in the United States. The steps required before a drug may be approved for marketing in the United States generally include:

- the completion of pre-clinical laboratory tests and animal tests conducted under GLP regulations;
- the submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical trials commence;

- the performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate for each proposed indication and conducted in accordance with cGCP;
- the submission to the FDA of a NDA;
- the FDA's acceptance of the NDA;
- satisfactory completion of an FDA inspection of the manufacturing facilities at which the product is made to assess compliance with cGMPs; and
- the FDA's review and approval of an NDA prior to any commercial marketing or sale of the drug in the United States.

The testing and approval process requires substantial time, effort and financial resources, and the receipt and timing of any approval is uncertain.

Pre-clinical studies include laboratory evaluations of the product candidate, as well as animal studies to assess the potential safety and efficacy of the product candidate. The results of the pre-clinical studies, together with manufacturing information and analytical data, are submitted to the FDA as part of the IND, which must become effective before clinical trials may be commenced. The IND will become effective automatically 30 days after receipt by the FDA, unless the FDA raises concerns or questions about the conduct of the trials as outlined in the IND prior to that time. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed.

Clinical trials involve the administration of the product candidates to healthy volunteers or patients with the disease to be treated under the supervision of a qualified principal investigator. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety, and the efficacy criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent IRB, either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, ethical factors, the safety of human subjects and the possible liability of the institution. There are also requirements governing the reporting of ongoing clinical trials and clinical trial results to public registries. The FDA, the IRB or the clinical trial sponsor may suspend or terminate clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the study. We may also suspend or terminate a clinical trial based on evolving business objectives and/or competitive climate.

Clinical trials typically are typically conducted in three sequential phases prior to approval, but the phases may overlap. These phases generally include the following:

- *Phase 1*. Phase 1 clinical trials represent the initial introduction of a product candidate into human subjects, frequently healthy volunteers. In Phase 1, the product candidate is usually tested for safety, including adverse effects, dosage tolerance, absorption, distribution, metabolism, excretion and pharmacodynamics.
- *Phase 2*. Phase 2 clinical trials usually involve studies in a limited patient population to (1) evaluate the efficacy of the product candidate for specific indications, (2) determine dosage tolerance and optimal dosage and (3) identify possible adverse effects and safety risks.
- *Phase 3*. If a product candidate is found to be potentially effective and to have an acceptable safety profile in Phase 2 studies, the clinical trial program will be expanded to Phase 3 clinical trials to further demonstrate clinical efficacy, optimal dosage and safety within an expanded patient population at geographically dispersed clinical study sites.

Phase 4 clinical trials are conducted after approval to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit in the case of drugs approved under accelerated approval regulations, or when otherwise requested by the FDA in the form of post-market requirements or commitments. Failure to promptly conduct any required Phase 4 clinical trials could result in withdrawal of approval.

The results of pre-clinical studies and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information on the manufacture, composition and quality of the product, are submitted to the FDA in the form of an NDA requesting approval to market the product. The NDA must be accompanied by a significant user fee payment. The FDA has substantial discretion in the approval process and may refuse to accept any application or decide that the data is insufficient for approval and require additional pre-clinical, clinical or other studies.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s).

Once the NDA submission has been submitted, the FDA has 60 days after submission of the NDA to conduct an initial review to determine whether it is sufficient to accept for filing. Under the Prescription Drug User Fee Act, the FDA sets a goal date by which it plans to complete its review. This is typically 12 months from the date of submission of the NDA application. The review process is often extended by FDA requests for additional information or clarification. Before approving an NDA, the FDA will inspect the facilities at which the product is manufactured and will not approve the product unless the manufacturing facility complies with cGMPs and may also inspect clinical trial sites for integrity of data supporting safety and efficacy. The FDA may also convene an advisory committee of external experts to provide input on certain review issues relating to risk, benefit and interpretation of clinical trial data. The FDA is not bound by the recommendations of an advisory committee, but generally follows such recommendations in making its decisions. The FDA may delay approval of an NDA if applicable regulatory criteria are not satisfied and/or the FDA requires additional testing or information. The FDA may require post-marketing testing and surveillance to monitor safety or efficacy of a product.

After the FDA evaluates the NDA and conducts inspections of manufacturing facilities where the drug product and/or its API will be produced, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, pre-clinical studies or manufacturing. Even if such additional information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. The FDA could also approve the NDA with a Risk Evaluation and Mitigation Strategy, or REMS, plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct one or more post-market studies or clinical trials. Such post-market testing may include Phase 4 clinical trials and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000, there is no reasonable expectation that sales of the drug in

the United States will be sufficient to offset the costs of developing and making the drug available in the United States. Orphan drug designation must be requested before submitting an NDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If the FDA approves a sponsor's marketing application for a designated orphan drug for use in the rare disease or condition for which it was designated, the sponsor is eligible for a seven-year period of marketing exclusivity, during which the FDA may not approve another sponsor's marketing application for a drug with the same active moiety and intended for the same use or indication as the approved orphan drug, except in limited circumstances, such as if a subsequent sponsor demonstrates its product is clinically superior. During a sponsor's orphan drug exclusivity period, competitors, however, may receive approval for drugs with different active moieties for the same indication as the approved orphan drug, or for drugs with the same active moiety as the approved orphan drug, but for different indications. Orphan drug exclusivity could block the approval of one of our products for seven years if a competitor obtains approval for a drug with the same active moiety intended for the same indication before we do, unless we are able to demonstrate that grounds for withdrawal of the orphan drug exclusivity exist, such as that our product is clinically superior. Further, if a designated orphan drug receives marketing approval for an indication broader than the rare disease or condition for which it received orphan drug designation, it may not be entitled to exclusivity.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including rare pediatric disease and breakthrough therapy designations, which are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

Rare pediatric disease, or RPD, designation by the FDA enables priority review voucher, or PRV, eligibility upon U.S. market approval of a designated drug for rare pediatric diseases. The RPD-PRV program is intended to encourage development of therapies to prevent and treat rare pediatric diseases. The voucher, which is awarded upon NDA or Biologics License Application, or BLA, approval to the sponsor of a designated RPD can be sold or transferred to another entity and used by the holder to receive priority review for a future NDA or BLA submission, which reduces the FDA review time of such future submission from ten to six months.

Breakthrough therapy designation is for a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Pharmaceutical Coverage, Pricing and Reimbursement

In both domestic and foreign markets, our sales of any approved products will depend in part on the availability of coverage and adequate reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. Patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use our products, if approved, unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Sales of our products will therefore depend substantially, both domestically and abroad, on the extent to which the costs of our products will be paid by third-party payors. These third-party payors are increasingly focused on containing healthcare costs by challenging the price and examining the cost-effectiveness of medical products and services.

In addition, significant uncertainty exists as to the coverage and reimbursement status of newly approved healthcare product candidates. The market for our product candidates for which we may receive regulatory approval will depend significantly on access to third-party payors' drug formularies, or lists of medications for which third-party payors provide coverage and reimbursement. The industry competition to be included in such formularies often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payors may refuse to include a particular branded drug in their formularies or otherwise restrict patient access to a branded drug when a less costly generic equivalent or other alternative is available. Furthermore, third-party payor reimbursement to providers for our product candidates may be subject to a bundled payment that also includes the procedure administering our products. To the extent there is no separate payment for our product candidates, there may be further uncertainty as to the adequacy of reimbursement amounts.

Because each third-party payor individually approves coverage and reimbursement levels, obtaining coverage and adequate reimbursement is a time-consuming, costly and sometimes unpredictable process. We may be required to provide scientific and clinical support for the use of any product to each third-party payor separately with no assurance that approval would be obtained, and we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost-effectiveness of our products. This process could delay the market acceptance of any product and could have a negative effect on our future revenues and operating results. We cannot be certain that our product candidates will be considered cost-effective. Because coverage and reimbursement determinations are made on a payor-by-payor basis, obtaining acceptable coverage and reimbursement from one payor does not guarantee the Company will obtain similar acceptable coverage or reimbursement from another payor. If we are unable to obtain coverage of, and adequate reimbursement and payment levels for, our product candidates from third-party payors, physicians may limit how much or under what circumstances they will prescribe or administer them and patients may decline to purchase them. This in turn could affect our ability to successfully commercialize our products and impact our profitability, results of operations, financial condition and future success.

Furthermore, in many foreign countries, particularly the countries of the European Union, the pricing of prescription drugs is subject to government control. In some non-U.S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the Company placing the medicinal product on the market. We may face competition for our product candidates from lower-priced products in foreign countries that have placed price controls on pharmaceutical products. In addition, there may be importation of foreign products that compete with our own products, which could negatively impact our profitability.

Healthcare Reform

In the United States and foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system that could affect our future results of operations as we begin to directly commercialize our products.

In particular, there have been and continue to be a number of initiatives at the U.S. federal and state level that seek to reduce healthcare costs. Initiatives to reduce the federal deficit and to reform healthcare delivery are increasing cost-containment efforts. We anticipate that Congress, state legislatures and the private sector will continue to review and assess alternative benefits, controls on healthcare spending through limitations on the growth of private health insurance premiums and Medicare and Medicaid spending, the creation of large insurance purchasing groups, price controls on pharmaceuticals and other fundamental changes to the healthcare delivery system. Any proposed or actual changes could limit or eliminate our spending on development projects and affect our ultimate profitability.

In the future, there may continue to be additional proposals relating to the reform of the United States healthcare system, some of which could further limit the prices we are able to charge for our products candidates, or the amounts of reimbursement available for our product candidates. If future legislation were to impose direct governmental price controls and access restrictions, it could have a significant adverse

impact on our business. Managed care organizations, as well as Medicaid and other government agencies, continue to seek price discounts. Some states have implemented, and other states are considering, price controls or patient access constraints under the Medicaid program, and some states are considering price-control regimes that would apply to broader segments of their populations that are not Medicaid-eligible. Due to the volatility in the current economic and market dynamics, we are unable to predict the impact of any unforeseen or unknown legislative, regulatory, payor or policy actions, which may include cost containment and healthcare reform measures. Such policy actions could have a material adverse impact on our profitability.

The federal Drug Supply Chain Security Act imposes obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing. Manufacturers will be required to provide certain information regarding the drug product to individuals and entities to which product ownership is transferred, label drug product with a product identifier, and keep certain records regarding the drug product. Further, under this new legislation, manufacturers will have drug product investigation, quarantine, disposition, and notification responsibilities related to counterfeit, diverted, stolen, and intentionally adulterated products, as well as products that are the subject of fraudulent transactions or which are otherwise unfit for distribution such that they would be reasonably likely to result in serious health consequences or death.

Organizational structure

The registrant corporation, Auris Medical Holding AG, has four wholly-owned subsidiaries which are each listed in Exhibit 21.1 to the registration statement of which this proxy statement/prospectus forms a part. We primarily operate our business out of our operating subsidiary Auris Medical AG.

Property, plants and equipment

Our headquarters are in Zug, Switzerland. We also lease approximately 5,900 square feet of office space in Basel, Switzerland. This property serves as the corporate headquarters of our principal operating subsidiary.

Legal Proceedings

From time to time we may become involved in legal proceedings that arise in the ordinary course of business. During the period covered by the financial statements contained herein, we have not been a party to or paid any damages in connection with litigation that has had a material adverse effect on our financial position.

On July 20, 2015, the USPTO declared Patent Interference No. 106,030 involving our issued U.S. patent No. 9,066,865 (the "'865 Patent") and Otonomy's U.S. patent application No. 13/848,636 (the "'636 Application"). The patent interference identified claims 1-9 in the '865 Patent as interfering with claims 38, 43 and 46-50 of the '636 Application. The '865 Patent discloses methods of treating inner or middle ear diseases with intratympanic injections of poloxamer-based compositions. The claims of the '865 Patent are directed to the use of fluoroquinolone antibiotics in poloxamer 407 compositions under certain specifications. On January 26, 2017, the USPTO issued a decision on the interference granting Auris benefit of priority. As a result of the decision, judgment was entered against Otonomy and all claims in the '636 Application were refused. In addition, claims 1-8 of the '865 Patent were cancelled as the result of the USPTO's determination that the written description of the specification lacked full scope support for treating middle or inner ear disease with fluoroquinolone. However, claim 9, which is directed to a method of treating viral and bacterial infections with intratympanic injection of a fluoroquinolone antibiotic in a poloxamer 407 composition under certain specifications, was affirmed. On March 27, 2017, Otonomy submitted a notice of appeal to the United States Court of Appeals for the Federal Circuit. To preserve its rights, Auris filed a notice of cross-appeal on April 5, 2017. Otonomy subsequently filed its opening brief on July 20, 2017, and Auris filed its principal and response brief on October 27, 2017. On January 5, 2018, Otonomy filed its opposition and reply brief. Auris filed its reply brief on February 2, 2018. On August 1, 2018, the United States Court of Appeals for the Federal Circuit reversed the USPTO Patent Trial and Appeal Board's determination of priority in our favor relating to the July 2015 USPTO declaration of patent interference (No. 106,030) involving our issued '865 Patent and the '636 Application. We believe that this ruling will not materially impact any of our development programs.