Otonomy, Inc.
Form 424B5
January 05, 2016
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**Filed Pursuant to Rule 424(b)(5)**
**Registration No. 333-206752**

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been declared effective by the Securities and Exchange Commission under the Securities Act of 1933, as amended. This preliminary prospectus supplement, together with the accompanying prospectus, is not an offer to sell these securities and is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion

Preliminary Prospectus Supplement Dated January 5, 2016

**PROSPECTUS SUPPLEMENT**

(To the Prospectus dated September 14, 2015)

**$100,000,000**

**Common Stock**

We are selling $100,000,000 of shares of our common stock.

Our common stock trades on The NASDAQ Global Select Market under the symbol OTIC. On January 4, 2016, the last reported sale price of our common stock on The NASDAQ Global Select Market was $26.03 per share.

We are an emerging growth company as defined under the federal securities laws and, as such, have elected to comply with certain reduced public company reporting requirements.

**Investing in our common stock involves risks that are described in the Risk Factors beginning on page S-7 of this prospectus supplement.**

| | Per Share | Total |
|---|---|---|
| Public offering price | $ | $ |
| Underwriting discounts and commissions[(1)] | $ | $ |
| Proceeds, before expenses, to us | $ | $ |

(1) We refer you to the section entitled Underwriting beginning on page S-55 of this prospectus supplement for additional information regarding total underwriting compensation.

The underwriters may also exercise its option to purchase up to an additional $15,000,000 of shares of common stock from us, at the public offering price, less the underwriting discounts and commissions, for 30 days after the date of this prospectus supplement.

Neither the Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

The shares will be ready for delivery on or about , 2016.

*Joint Book-Running Managers*

**BofA Merrill Lynch** **Cowen and Company** **Piper Jaffray**

*Co-Managers*

**Bernstein** **SunTrust Robinson Humphrey**

The date of this prospectus supplement is January , 2016.

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### Prospectus Supplement



### Prospectus

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## ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus dated September 14, 2015 form part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission (SEC), utilizing a shelf registration process. This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date for example, a document incorporated by reference in the accompanying prospectus the statement in the document having the later date modifies or supersedes the earlier statement.

Neither us nor the underwriters have authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus or any free writing prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus or any free writing prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein or therein or any free writing prospectus is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any free writing prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein or any free writing prospectus, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled Where You Can Find More Information and Information Incorporated by Reference in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus or any free writing prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus or any free writing prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus or any free writing prospectus outside the United States.

Unless the context requires otherwise, references in this prospectus supplement to Otonomy, the Company, we, us a our refer to Otonomy, Inc.

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## PROSPECTUS SUPPLEMENT SUMMARY

*This summary description about us and our business highlights selected information contained elsewhere in this prospectus supplement or incorporated by reference in this prospectus supplement and the accompanying prospectus. This summary does not contain all of the information that you should consider before deciding to invest in our common stock. You should carefully read this entire prospectus supplement, the accompanying prospectus and any related free writing prospectus, including each of the documents incorporated herein or therein by reference, before making an investment decision. Investors should carefully consider the information set forth under Risk Factors in this prospectus supplement beginning on page S-7 and in any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus supplement. You also should carefully read the information incorporated by reference into this prospectus supplement, including our financial statements, other information and the exhibits to the registration statement of which the accompanying prospectus is a part.*

### Overview

Otonomy is a biopharmaceutical company focused on the development and commercialization of innovative therapeutics for diseases and disorders of the ear. OTIPRIO (ciprofloxacin otic suspension) is the first drug approved in the United States (US) for use during tympanostomy tube placement (TTP) surgery and commercial launch is expected in the first quarter of 2016. OTIPRIO is also being evaluated for potential label expansion in acute otitis externa (also known as swimmer s ear ) and acute otitis media with tympanostomy tube (AOMT). OTO-104 is a steroid in development for the treatment of Ménière s disease and other balance and hearing disorders. A Phase 3 trial in Ménière s disease patients has been initiated in the United States with a second trial expected to be initiated in the European Union (EU) during the first quarter of 2016. OTO-311 is a N-Methyl-D-Aspartate (NMDA) receptor antagonist for the treatment of tinnitus that is currently in a Phase 1 clinical safety trial. A fourth program targeting sensorineural hearing loss including age-related hearing loss is in preclinical development. OTIPRIO and our current product candidates utilize our proprietary formulation technology that combines a thermosensitive gel with drug microparticles to enable a single dose treatment by a physician.

The following graphic summarizes the status of our product and product candidate pipeline:

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**OTIPRIO (ciprofloxacin otic suspension)**

OTIPRIO, a single-dose, physician-administered antibacterial, was approved by the U.S. Food and Drug Administration (FDA) in December 2015 and is the only product approved for the treatment of pediatric patients with bilateral otitis media with effusion undergoing TTP surgery. In two Phase 3 trials with a combined total of 532 pediatric patients, a single intraoperative administration of OTIPRIO demonstrated a statistically significant reduction in the cumulative proportion of study treatment failures compared to tubes alone (p-value <0.001). We expect to launch OTIPRIO in the United States in the first quarter of 2016.

According to the American Academy of Otolaryngology Head and Neck Surgery Foundation, TTP surgery is the most common ambulatory surgery performed on children. Overall, there are approximately one million TTP procedures performed each year in the United States of which 85% are in pediatric patients, who typically have middle ear effusion and receive tubes in both ears (bilateral). The tubes are placed for the treatment of persistent or recurrent otitis media (infection and/or inflammation of the middle ear). Placement of the tube helps to ventilate the middle ear and enables the administration of topical antibiotics to treat the infection.

We plan to commercialize OTIPRIO using an internal sales force targeting the approximately 2,000 physicians and 800 facilities that we estimate account for nearly 70% of TTP surgeries in the United States. We plan to address this target audience by hiring approximately 40 sales representatives who are experienced in healthcare product sales including hospital-based products. We have also hired a team of field-based medical science liaisons (MSLs) and expect that they will play an important role in providing medical information about OTIPRIO to clinicians and other health care professionals.

We are also evaluating OTIPRIO for potential label expansion in acute otitis externa and AOMT. We have completed a Phase 2 clinical trial in 75 patients with acute otitis externa that demonstrated technical feasibility of administration and a clinical cure rate of greater than 80% for patients treated with a 0.2 mL dose. We intend to meet with the FDA to discuss the requirements for a registration program for OTIPRIO in this indication. We have also completed a Phase 2 clinical trial in 39 pediatric patients with AOMT and intend to initiate a second Phase 2 clinical trial in the first quarter of 2016 in this patient population to identify the preferred dose for further development.

We have global commercialization rights to OTIPRIO with patent protection in the United States until 2035, and we are evaluating whether to develop and, if approved, commercialize OTIPRIO outside the United States on our own or in collaboration with partners.

**OTO-104: Sustained-Exposure Steroid for Inner Ear Disorders**

OTO-104 is a sustained-exposure formulation of the steroid dexamethasone in development for the treatment of Ménière s disease and other inner ear conditions. Ménière s disease is a chronic condition characterized by acute vertigo attacks, tinnitus, fluctuating hearing loss and a feeling of aural fullness. The underlying cause of Ménière s disease is not well understood and there is no known cure. There are more than 600,000 patients diagnosed with Ménière s disease in the United States and there are currently no FDA-approved drug treatments. Typical first line treatment in the United States is observance of a low-salt diet and off-label use of diuretics. Oral and intratympanic (IT) steroids are used in a subset of Ménière s patients who have persistent or severe symptoms. Patients who are unresponsive to steroid treatment may resort to surgical or chemical ablation, which can cause irreversible hearing loss.

In May 2015, we announced results from a Phase 2b clinical trial evaluating OTO-104 in 154 patients with unilateral Ménière s disease. The primary endpoint of the clinical trial was reduction in vertigo frequency

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during Month 3 following treatment compared to a one month baseline period. In the topline analysis, OTO-104 demonstrated a 61% reduction from baseline in vertigo frequency in Month 3 vs. 43% for placebo with a p value of 0.067, which narrowly missed achieving statistical significance. The clinical trial achieved statistical significance ($p < 0.05$) for multiple prospectively defined secondary vertigo endpoints at multiple time points including the count of Definitive Vertigo Days (DVD) that achieved statistical significance in both Month 3 ($p = 0.030$) and Month 2 ($p = 0.035$). Based on these results, and discussions with the FDA during an End-of-Phase 2 meeting, we intend to conduct two parallel Phase 3 clinical trials in Ménière s disease using DVD during Month 3 as the primary endpoint. The first Phase 3 clinical trial has recently been initiated in the United States and a second clinical trial is expected to be initiated in the European Union during the first quarter of 2016. Results of both Phase 3 clinical trials are expected in the second half of 2017. Patients completing the Phase 3 clinical trials will also have the opportunity to enroll in an open-label clinical safety trial and receive two quarterly doses of OTO-104. If successful, we expect to submit a New Drug Application (NDA) for OTO-104 to the FDA in the first half of 2018.

In April 2015, we announced the completion of enrollment in a multiple-dose clinical safety trial of OTO-104 in patients with Ménière s disease in the United Kingdom (UK). This clinical trial is designed to evaluate the safety of quarterly dosing of OTO-104. The clinical trial enrolled a total of 128 Ménière s patients across multiple trial sites in the United Kingdom. We plan to initiate a small open-label clinical safety trial of OTO-104 in Canada to supplement the number of patients treated for one year in the multiple-dose UK clinical safety trial.

OTO-104 for Ménière s disease has been granted Fast Track designation by the FDA. We plan to assess and prioritize additional opportunities for OTO-104 including other balance disorders, acute onset sensorineural hearing loss and tinnitus.

**OTO-311: Sustained-Exposure Treatment for Tinnitus**

OTO-311 is a sustained-exposure formulation of the NMDA receptor antagonist gacyclidine in development for the treatment of tinnitus. Tinnitus is often described as a ringing in the ear but can also sound like roaring, clicking, hissing or buzzing. People with severe tinnitus may have trouble hearing, working and sleeping. At this time, there is no cure for tinnitus and there are no FDA-approved drugs for the treatment of this debilitating condition.

Historic and emerging clinical data provide support for the use of NMDA receptor antagonists, including gacyclidine, for the treatment of tinnitus. Mechanistically, agents from this therapeutic class may act to reduce dysfunctional activity resulting from injury to the hearing organ, or cochlea, and be perceived by the patient as tinnitus. For example, Phase 2 clinical trials with several agents have demonstrated reductions in the severity of tinnitus and improvement in the functional status of treated patients. We expect that the results of these clinical trials will be instructive in the design and implementation of our clinical development program.

The goal of our OTO-311 program is to develop a sustained-exposure formulation of gacyclidine that will provide a full course of treatment from a single IT injection. In November 2015, we initiated a Phase 1 dose escalation clinical safety trial in normal healthy volunteers. OTO-311 will be given as a single unilateral IT injection and subjects will be observed for four weeks following dosing. We expect this clinical trial to be completed in the first half of 2016, with a Phase 2 clinical trial in tinnitus patients expected to begin in the second half of 2016.

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**Program 4: Treatment for Sensorineural Hearing Loss**

We have acquired the rights to multiple product candidates for our fourth development program, which will target age-related hearing loss, also known as presbycusis.

According to the National Institute on Deafness and Other Communication Disorders, there are 36 million adults in the United States who report hearing loss, which we believe represents the largest market opportunity in the otology field. We are evaluating several different approaches to treat this condition, including repair of damaged ribbon synapses and regeneration of cochlear hair cells. Formulation and preclinical development is underway.

**Our Proprietary Otic Drug Delivery Technology**

To overcome many of the limitations of delivering drugs to the ear, we have developed a proprietary technology that is designed to deliver drug that is retained in the ear for an extended period of time following a single local administration, which we refer to as sustained-exposure. Our technology utilizes a thermosensitive polymer vehicle, which transitions from a liquid to a gel at body temperature. The polymer vehicle is combined with drug microparticles to create a suspension that is retained in the ear for an extended period of time. This prolonged residence time provides high and sustained drug exposure.

Potential benefits for our product and product candidates include:

- Single local administration.
- High drug levels in the target location and minimal systemic exposure.
- Eliminates the need for the patient to remain in a prone position for an extended period of time.
- Simple, office-based administration by an ear, nose and throat physician (ENT).
- Avoids patient compliance concerns.

We have a broad patent portfolio of approximately 75 issued patents and allowed patent applications and at least 90 pending patent applications covering our product, product candidates and indications as well as other potential applications of our technology in major markets around the world.

**Recent Developments**

OTIPRIO was approved by the FDA in December 2015 and is the only product approved for the treatment of pediatric patients with bilateral otitis media with effusion undergoing TTP surgery. We expect to launch OTIPRIO in the United States in the first quarter of 2016.

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## Corporate and Other Information

Our principal executive offices are located at 6275 Nancy Ridge, Suite 100, San Diego, California 92121, and our telephone number is (858) 242-5200. Our website is www.otonomy.com. Information contained on, or that can be accessed through, our website is not incorporated by reference into this prospectus supplement or the accompanying prospectus, and you should not consider information on our website to be part of this prospectus supplement or the accompanying prospectus. We were incorporated in Delaware in May 2008.

Otonomy, the Otonomy logo and other trademarks or service marks of Otonomy appearing in this prospectus supplement and the accompanying prospectus are the property of Otonomy. Trade names, trademarks and service marks of other companies appearing in this prospectus are the property of their respective holders. We have omitted the ® and ™ designations, as applicable, for the trademarks used in this prospectus supplement and the accompanying prospectus.

We are an emerging growth company as defined in the Jumpstart Our Business Startups Act of 2012 (JOBS Act). We will remain an emerging growth company until the earliest to occur of: the last day of the fiscal year in which we have more than $1.0 billion in annual revenue; the date we qualify as a large accelerated filer, with at least $700 million of equity securities held by non-affiliates; the issuance, in any three-year period, by us of more than $1.0 billion in non-convertible debt securities; and the last day of the fiscal year ending after the fifth anniversary of our initial public offering, or December 31, 2019. As a result of this status, we have taken advantage of reduced reporting requirements in this prospectus supplement and the accompanying prospectus. In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards, delaying the adoption of these accounting standards until they would apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, as a result, we have and will continue to adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

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**The Offering**

| | |
|---|---|
| Common stock offered by us | shares. |
| Common stock to be outstanding after this offering | shares. |
| Option to purchase additional shares | shares. |
| Use of proceeds | We intend to use the net proceeds from this offering to fund expenses in connection with commercializing OTIPRIO in the United States and conducting clinical trials for OTIPRIO in one or more potential expansion indications; OTO-104 clinical development, including completion of the U.S. Phase 3 clinical trial, initiation and completion of an EU Phase 3 clinical trial, and initiation and completion of one or more open-label, multiple-dose safety studies in Ménière s patients; completion of a Phase 1 clinical safety trial for OTO-311 and, based on the results, initiation and completion of a Phase 2 clinical trial in tinnitus patients; and for research and development activities including preclinical development of Program 4 targeting sensorineural hearing loss, working capital, facilities expansion and other general corporate purposes. See Use of Proceeds. |
| NASDAQ Global Select Market symbol | OTIC. |

The number of shares of our common stock to be outstanding after this offering is based on 24,235,769 shares of common stock outstanding as of September 30, 2015, and excludes:

- 3,354,274 shares of common stock issuable upon the exercise of options outstanding as of September 30, 2015, at a weighted-average exercise price of $14.3394 per share;
- 141,060 shares of common stock issuable upon the exercise of outstanding warrants to purchase shares of common stock as of September 30, 2015, at an exercise price of $14.1765 per share of common stock subject to such warrants;
- 2,261,396 shares of common stock reserved for future issuance under our 2014 Equity Incentive Plan (2014 Plan) as of September 30, 2015, and any additional shares that become available under our 2014 Plan pursuant to provisions thereof that automatically increase the share reserve under the plan each year; and

672,182 shares of common stock reserved for future issuance under our 2014 Employee Stock Purchase Plan (ESPP), as of September 30, 2015, and any additional shares that become available under our ESPP pursuant to provisions thereof that automatically increase the share reserve under the plan each year.

Unless otherwise noted, the information in this prospectus supplement reflects and assumes no exercise of outstanding options or warrants to purchase common stock after September 30, 2015, and no exercise by the underwriters of their option to purchase additional shares of our common stock in this offering.

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## RISK FACTORS

*Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below, as well as all other information included in this prospectus supplement, the accompanying prospectus and in our other filings with the SEC before you decide to purchase shares of our common stock. If any of the following risks actually occurs, our business, financial condition, operating results, prospects and ability to accomplish our strategic objectives could be materially harmed. As a result, the trading price of our common stock could decline and you could lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations and the market price of our common stock.*

### Risks Related to Our Financial Condition and Capital Requirements

***We have a limited operating history and have incurred significant losses since our inception, and we anticipate that we will continue to incur losses for the foreseeable future, which makes it difficult to assess our future viability.***

We are a commercial-stage biopharmaceutical company with a limited operating history upon which you can evaluate our business and prospects. We are not profitable and have incurred losses in each year since we commenced operations in 2008. In addition, we have limited experience and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical industry. Drug development is a highly speculative undertaking and involves a substantial degree of risk. To date, we have obtained U.S. regulatory approval for only one product, have not yet commercialized any of our products and have not generated any revenue. We continue to incur significant research and development expenses related to our ongoing clinical trials and product development activities, commercialization expenses to prepare for our launch of OTIPRIO in the U.S. market, and other general and administrative expenses. We have recorded net losses of $16.0 million and $12.0 million for the three months ended September 30, 2015 and 2014, respectively, and $40.5 million and $33.1 million for the nine months ended September 30, 2015 and 2014, respectively. As of September 30, 2015, we had an accumulated deficit of $143.0 million.

***We have not yet generated product revenue and may never become profitable.***

We expect to continue to incur significant losses for the foreseeable future. Our ability to achieve revenue and profitability is dependent on our ability to complete the development of our product candidates, obtain necessary regulatory approvals and successfully commercialize our products. We may never succeed in these activities and therefore may never generate revenue that is significant or large enough to achieve profitability. Even if we achieve profitability in the future, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders equity and working capital and any failure to become and remain profitable may adversely affect the market price of our common stock, our ability to raise capital, and our viability.

***We may require additional financing to commercialize OTIPRIO and to obtain regulatory approval for OTO-104, OTO-311 and any other product candidates, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our commercialization efforts, product development, or other operations.***

Since our inception, most of our resources have been dedicated to the development of OTIPRIO and our product candidates, OTO-104 and OTO-311. In particular, commercializing OTIPRIO, and commencing and completing clinical trials for OTO-104 and OTO-311, will require substantial funds. We have funded our operations primarily

through the sale and issuance of common stock, convertible preferred stock and convertible notes. As of September 30, 2015, we had cash, cash equivalents and short-term investments of $199.2 million.

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We believe that we will continue to expend substantial resources for the foreseeable future for the commercialization of OTIPRIO and the development of OTO-104, OTO-311 and any other product candidates we may choose to pursue. These expenditures will include costs associated with marketing and selling any products approved for sale, manufacturing, preparing regulatory submissions, and conducting preclinical studies and clinical trials. We cannot estimate with reasonable certainty the actual amounts necessary to successfully commercialize OTIPRIO or complete the development and commercialization of our product candidates.

Our future capital requirements depend on many factors, including:

- the cost of commercialization activities for OTIPRIO and our other products that may be approved for sale, if any, including marketing, sales and distribution costs and related facilities expansion costs;
- the timing of, and the costs involved in, clinical development and obtaining regulatory approvals for OTO-104, OTO-311 or any future product candidates;
- the cost of manufacturing our products;
- the number and characteristics of any other product candidates we develop or acquire;
- our ability to establish and maintain strategic collaborations, licensing or other commercialization arrangements and the terms and timing of such arrangements;
- the degree and rate of market acceptance of any approved products;
- the emergence, approval, availability, perceived advantages, relative cost, relative safety and relative efficacy of other products or treatments;
- the expenses needed to attract and retain skilled personnel;
- the costs associated with being a public company;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patent claims, including litigation costs and the outcome of such litigation;
- the timing, receipt and amount of sales of, or royalties on, future approved products, if any; and

any product liability or other lawsuits related to our products.

Additional capital may not be available when we need it, on terms that are acceptable to us or at all. If adequate funds are not available to us on a timely basis, we may be required to delay, limit, reduce or terminate our establishment of sales and marketing, manufacturing or distribution capabilities or other activities that may be necessary to commercialize our product or product candidates, preclinical studies, clinical trials or other development activities.

If we raise additional capital through marketing and distribution arrangements or other collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish certain valuable rights to our product or product candidates, technologies, future revenue streams or research programs or grant licenses on terms that may not be favorable to us. If we raise additional capital through public or private equity offerings, the ownership interest of our existing stockholders will be diluted and the terms of any new equity securities may have preferential rights over our common stock. If we raise additional capital through debt financing, we may be subject to covenants limiting or restricting our ability to take specific actions, such as incurring additional debt or making capital expenditures or specified financial ratios, any of which could restrict our ability to commercialize our product, develop and commercialize our product candidates or operate as a business.

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**Risks Related to Our Product and Product Candidates**

***We are substantially dependent on the commercial success of OTIPRIO.***

To date, we have invested substantial resources in the development of OTIPRIO, which is our only product that has obtained regulatory approval from the FDA. We have not yet begun to commercialize OTIPRIO and have not yet manufactured OTIPRIO for commercial sale.

The future success of OTIPRIO, including the anticipated timing of the commercial launch of OTIPRIO in the United States, is primarily subject to the risks associated with manufacturing and commercialization, including risks associated with:

- our ability to validate the process used to manufacture OTIPRIO for commercial use;
- the ability to manufacture sufficient commercial supplies of OTIPRIO in compliance with current Good Manufacturing Practices;
- our ability to build an effective sales organization to market OTIPRIO;
- our success in educating physicians, patients and caregivers about the benefits, administration and use of OTIPRIO;
- the availability, perceived advantages, relative cost, relative safety and relative efficacy of other products or treatments for middle ear effusion at the time of TTP surgery, particularly the off-label use of multi-dose, multi-day antibiotic ear drops;
- the demand for the treatment of middle ear effusion in patients requiring TTP surgery which is subject to seasonality, with higher volume in September through May;
- the availability of coverage and adequate reimbursement for OTIPRIO;
- our ability to obtain a J-Code and C-Code for OTIPRIO and the willingness of third-party payors to reimburse OTIPRIO based on the J-Code or C-Code;
- the successful completion of clinical trials, regulatory approval, and commercialization of OTIPRIO for one or more label expansion indications;

our ability to enforce our intellectual property rights in and to OTIPRIO; and

a continued acceptable safety profile of OTIPRIO following approval.

Many of these clinical, regulatory and commercial matters are beyond our control and are subject to other risks described elsewhere in this Risk Factors section. Accordingly, we cannot assure you that we will be able to successfully manufacture, commercialize, or generate significant revenue from OTIPRIO, or obtain regulatory approval in label expansion indications for OTIPRIO. If we cannot do so, or are significantly delayed in doing so, our business will be materially harmed.

***We are also dependent upon the clinical, regulatory and commercial success of OTO-104.***

In addition to OTIPRIO, we have also invested substantial resources in the development of OTO-104. In May 2015, we announced results from a Phase 2b clinical trial evaluating OTO-104 in patients with unilateral Ménière s disease, which narrowly missed achieving statistical significance for the primary endpoint. We

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completed our End-of-Phase 2 meeting with the FDA and expect to conduct two parallel Phase 3 clinical trials in Ménière s disease, with the first clinical trial initiated in the United States in November 2015 and the second clinical trial expected to be initiated in the European Union during the first quarter of 2016. We have completed enrollment in a multiple-dose clinical safety trial for OTO-104 in Ménière s patients in the United Kingdom and plan to initiate one or more additional multiple-dose safety studies during 2016 to satisfy our multiple-dose clinical safety requirement for U.S. regulatory approval of OTO-104 in Ménière s patients.

Given the stage of development of OTO-104, it is currently most subject to the risks associated with completing its current clinical trials and future clinical trials, including risks associated with:

- the successful implementation, enrollment and completion of two parallel Phase 3 clinical trials that demonstrate the safety and efficacy of OTO-104;
- the use and adequacy of patient reported outcomes in our Phase 3 clinical trials;
- our ability to demonstrate with substantial clinical evidence the safety and efficacy of OTO-104 in these clinical trials;
- the successful implementation, enrollment and completion of one or more additional open-label safety studies and the ongoing multiple-dose clinical safety trial in the United Kingdom; and
- the ability to submit an NDA for regulatory approval to the FDA without the need for any additional clinical trials.

If we are able to successfully complete the necessary clinical trials for OTO-104, its success will still remain subject to the risks associated with obtaining regulatory approval from the FDA and being manufactured and commercialized, including risks associated with:

- the successful completion of all non-clinical studies required to support regulatory approval by the FDA;
- the timing of review, as the FDA s grant of Fast Track designation for OTO-104 does not guarantee priority review;
- the FDA s acceptance of our NDA submission for OTO-104;
- the successful and timely receipt of necessary marketing approval from the FDA to allow us to begin commercializing OTO-104 in the United States;

the ability to manufacture commercial supplies of OTO-104 in compliance with current Good Manufacturing Practices;

the ability of our future sales organization to sell OTO-104;

our success in educating physicians and patients about the benefits, administration and use of OTO-104;

the availability, perceived advantages, relative cost, relative safety and relative efficacy of other products or treatments for Ménière s disease;

patient demand for the treatment of Ménière s disease;

the availability of coverage and adequate reimbursement for OTO-104;

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our ability to enforce our intellectual property rights in and to OTO-104; and

a continued acceptable safety profile of OTO-104 following approval.

Many of these clinical, regulatory and commercial matters are beyond our control and are subject to other risks described elsewhere in this Risk Factors section. Accordingly, we cannot assure you that we will be able to advance OTO-104 further through final clinical development, or obtain regulatory approval of, manufacture, commercialize or generate significant revenue from OTO-104. If we cannot do so, or are significantly delayed in doing so, our business will be materially harmed.

***In addition to OTIPRIO and OTO-104, our long-term prospects depend in part upon advancing additional product candidates, such as OTO-311, through clinical development to regulatory approval and commercialization.***

Although we are focused upon commercialization of OTIPRIO and completion of the clinical trials and potential regulatory approval and commercialization of OTO-104, the development of OTO-311 and other potential candidates for the treatment of inner and middle ear disorders is a key element of our long-term strategy. We have recently initiated a Phase 1 clinical safety trial for OTO-311, and we have acquired the rights to multiple product candidates for our fourth development program, which will target age-related hearing loss. Therefore, these programs are currently most subject to the risks associated with preclinical and clinical development, including the risks associated with:

generating sufficient data to support the initiation or continuation of clinical trials;

obtaining regulatory approval to commence clinical trials;

contracting with the necessary parties to conduct clinical trials;

enrolling sufficient numbers of subjects or patients in clinical trials;

the timely manufacture of sufficient quantities of the product candidate for use in clinical trials; and

adverse events in the clinical trials.

Even if we successfully advance OTO-311 through clinical development, or advance product candidates from our fourth development program or any other future product candidate into clinical development, their success will be subject to all of the clinical, regulatory and commercial risks described elsewhere in this Risk Factors section. Accordingly, we cannot assure you that we will ever be able to develop, obtain regulatory approval of, commercialize or generate significant revenue from OTO-311, any product candidate from our fourth development program or any other future product candidate.

**Risks Related to Our Business and Strategy**

***OTIPRIO and our product candidates, OTO-104, OTO-311, or any future product candidates that obtain regulatory approval, may fail to achieve the broad degree of market acceptance and use necessary for commercial success.***

OTIPRIO and our product candidates, if approved, may not achieve market acceptance among physicians and patients, and may not be commercially successful. There are currently no FDA-approved drug treatments for the indications we are pursuing. Treatment of pediatric patients with bilateral otitis media with effusion undergoing TTP surgery, our approved indication for OTIPRIO, is currently addressed with the off-label use of antibiotic ear drops. Our proposed indication for OTO-104 is the treatment of vertigo associated with

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Ménière s disease. Currently, Ménière s disease patients are routinely prescribed a low-salt diet and off-label use of diuretics. Physicians may also prescribe the off-label use of antihistamines, anticholinergics, phenothiazines and benzodiazepines as well as corticosteroids. Our proposed indication for OTO-311 is the treatment of tinnitus. Currently, physicians may attempt to treat tinnitus symptoms with the off-label use of steroids, anxiolytics, antidepressants, and antipsychotics. The commercial success of OTIPRIO and our product candidates, if approved, will depend significantly on the adoption and use of the resulting product by physicians for approved indications. The decision to elect treatment with OTIPRIO for middle ear effusion in pediatric patients requiring TTP surgery, or to elect to utilize OTO-104 for Ménière s disease or OTO-311 for tinnitus, rather than other products or treatments, may be influenced by a number of factors, including:

- the cost, safety and effectiveness of our products as compared to other products or treatments;
- physician willingness to adopt a new treatment in lieu of other products or treatments;
- the extent to which physicians recommend our products to their patients;
- patient or caregiver sentiment about the benefits and risks of our products;
- proper training and administration of our products by physicians and medical staff, such that their patients do not experience excessive discomfort during treatment or adverse side effects;
- the procedural risks of IT injection, including persistent injection site perforation of the tympanic membrane, which has occurred in our OTO-104 Phase 1b and Phase 2b clinical trials;
- overcoming any biases physicians or patients may have in favor of other products or treatments;
- patient preference for non-injectable treatments;
- patient or caregiver satisfaction with the results and administration of our product and overall treatment experience, including relative convenience and ease of administration;
- the effectiveness of our sales and marketing efforts;
- demand for the treatment of the relevant diseases or disorders;

product labeling or product insert requirements of the FDA or other regulatory authorities;

the prevalence and severity of any adverse events;

the revenue and profitability that our products will offer a physician as compared to other products or treatments;

the availability of coverage and adequate reimbursement by third-party payors and government authorities; and

general patient or caregiver confidence, which may be impacted by economic and political conditions.

If OTIPRIO or our product candidates, if approved for use, fail to achieve the broad degree of market acceptance necessary for commercial success, our operating results and financial condition will be adversely affected. In addition, even if any of our products gain acceptance, the markets for treatment of patients with our target indications may not be as significant as we estimate.

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***Clinical drug development involves a lengthy and expensive process with an uncertain outcome, results of earlier studies and trials may not be predictive of future trial results, and our clinical trials may fail to adequately demonstrate the safety and efficacy of our product candidates.***

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. A failure of one or more of our clinical trials can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. There is a high failure rate for drugs proceeding through clinical trials, and product candidates in later stages of clinical trials may fail to show the required safety and efficacy despite having progressed through preclinical studies and initial clinical trials. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier clinical trials, and we cannot be certain that we will not face similar setbacks. Even if our clinical trials are completed, the results may not be sufficient to obtain regulatory approval for our product candidates or support the indications which we are pursuing.

We have in the past experienced delays in our ongoing clinical trials and we may in the future. We do not know whether future clinical trials, if any, will begin on time, need to be redesigned, enroll an adequate number of patients on time or be completed on schedule, if at all. Clinical trials can be delayed, suspended or terminated for a variety of reasons, including failure to:

- generate sufficient preclinical, toxicology, or other in vivo or in vitro data to support the initiation or continuation of clinical trials;
- obtain regulatory approval, or feedback on trial design, to commence a clinical trial;
- identify, recruit and train suitable clinical investigators;
- reach agreement on acceptable terms with prospective contract research organizations (CROs), and clinical trial sites;
- obtain and maintain institutional review board (IRB), approval at each clinical trial site;
- identify, recruit and enroll suitable patients to participate in a clinical trial;
- have a sufficient number of patients complete a clinical trial or return for post-treatment follow-up;
- ensure clinical investigators observe trial protocol and comply with Good Clinical Practices or continue to participate in a clinical trial;

address any patient safety concerns that arise during the course of a clinical trial;

address any conflicts with new or existing laws or regulations;

add a sufficient number of clinical trial sites;

timely manufacture sufficient quantities of product candidate for use in clinical trials; or

raise sufficient capital to fund a clinical trial.

Patient enrollment is a significant factor in the timing of clinical trials and is affected by many factors, including the size and nature of the patient population, the proximity of patients to clinical sites, the eligibility criteria for the clinical trial, the design of the clinical trial, competing clinical trials and clinicians and patients

or caregivers perceptions as to the potential advantages of the drug candidate being studied in relation to other available therapies, including any new drugs or treatments that may be approved for the indications we are investigating.

We could also encounter delays if a clinical trial is suspended or terminated by us, by the data safety monitoring board for such clinical trial or by the FDA or any other regulatory authority, or if the IRBs of the institutions in which such clinical trials are being conducted suspend or terminate the participation of their clinical investigators and sites subject to their review. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

OTO-104 was previously subject to Full Clinical Hold that was removed in July 2013 and then subject to Partial Clinical Hold that was removed in June 2014. The removal of Full Clinical Hold allowed us to initiate the Phase 2b clinical trial. As a result of OTO-104 being placed on Full Clinical Hold, OTIPRIO was also placed on Full Clinical Hold. The OTIPRIO Full Clinical Hold was removed in November 2012. We cannot assure you that our product candidates will not be subject to new clinical holds or significant delay in the future.

If we experience delays in the initiation or completion of any clinical trial of our product candidates for any reason, or if any clinical trial is terminated, the commercial prospects of our product candidates may be harmed, and our ability to generate product revenues from any of these product candidates will be delayed. In addition, 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 significantly harm our business, financial condition and prospects. 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 be unable to obtain regulatory approval for our product candidates other than OTIPRIO. The denial or delay of any such approval would delay commercialization and have a material adverse effect on our potential to generate revenue, our business and our results of operations.***

The research, development, testing, manufacturing, labeling, packaging, approval, promotion, advertising, storage, recordkeeping, marketing, distribution, post-approval monitoring and reporting, and export and import of drug products are subject to extensive regulation by the FDA, and by foreign regulatory authorities in other countries. These regulations differ from country to country. To gain approval to market our product candidates, we must provide clinical data that demonstrates with substantial evidence the safety and efficacy of the product for the intended indication. Other than OTIPRIO in the United States, we have not yet obtained regulatory approval to market any of our other product candidates in the United States or any other country. Our business depends upon obtaining these regulatory approvals.

The FDA can delay, limit or deny approval of our product candidates for many reasons, including:

- our inability to satisfactorily demonstrate that the product candidates are safe and effective for the requested indication;

the FDA s disagreement with our trial protocol or the interpretation of data from preclinical studies or clinical trials;

the population studied in the clinical trial may not be sufficiently broad or representative to assess safety in the full population for which we seek approval;

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our inability to demonstrate that clinical or other benefits of our product candidates outweigh any safety or other perceived risks;

the FDA s determination that additional preclinical or clinical trials are required;

the FDA s non-approval of the formulation, labeling or the specifications of our product candidates;

the FDA s failure to accept the manufacturing processes or facilities of third-party manufacturers with which we contract, or our inability to manufacture our product candidates pursuant to current Good Manufacturing Practices; or

the potential for approval policies or regulations of the FDA to significantly change in a manner rendering our clinical data insufficient for approval.

Even if we eventually complete clinical testing and re