OTONOMY, INC.
Form 10-K
March 02, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2016

OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
FOR THE TRANSITION PERIOD FROM TO

Commission File Number 001-36591

Otonomy, Inc.

(Exact name of registrant as specified in its Charter)

Delaware	26-2590070
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

4796 Executive Drive

San Diego, California 92121

(Address of principal executive offices and Zip Code)

(619) 323-2200

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
Common stock, par value $0.001 per share	The NASDAQ Stock Market LLC
	(The NASDAQ Global Select Market)

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES NO

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. YES NO

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES NO

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). YES NO

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definition of "large accelerated filer", "accelerated filer", and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer		Accelerated filer
Non-accelerated filer	(Do not check if a smaller reporting company)	Smaller reporting company

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES NO

The aggregate market value of the common stock held by non-affiliates of the registrant as of June 30, 2016 (the last business day of the registrant's most recently completed second fiscal quarter) was approximately $323.9 million based on the closing price of the registrant's common stock, as reported by the NASDAQ Global Select Market on June 30, 2016 of $15.88 per share. Shares of the registrant's common stock held by each executive officer, director and holder of 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This calculation does not reflect a determination that certain persons are affiliates of the registrant for any other purpose.

As of February 24, 2017 the number of outstanding shares of the registrant's common stock, par value $0.001 per share, was 30,256,879.

DOCUMENTS INCORPORATED BY REFERENCE

As noted herein, the information called for by Part III is incorporated by reference to specified portions of the registrant's definitive proxy statement to be filed in conjunction with the registrant's 2017 Annual Meeting of Stockholders, which is expected to be filed not later than 120 days after the Registrant's fiscal year ended December 31, 2016.

OTONOMY, INC.

ANNUAL REPORT ON FORM 10-K

FOR THE YEAR ENDED DECEMBER 31, 2016

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, as Section 21E of the Securities Exchange Act of 1934, as amended, which statements involve substantial risks and uncertainties. Forward-looking statements generally relate to future events or our future financial or operating performance. In some cases, you can identify forward-looking statements because they contain words such as “anticipate,” “believe,” “could,” “estimate,” “expects,” “intend,” “may,” “plan,” “potential,” “predi “should,” “will,” “would” the negative of those terms, and similar expressions that convey uncertainty of future events or outcomes. Forward-looking statements contained in this Annual Report on Form 10-K include, but are not limited to, statements about:

- our expectations regarding our clinical development and commercialization of OTIPRIO;
- our expectations regarding our clinical development of OTO-104, including but not limited to obtaining results for both the AVERTS-1 and AVERTS-2 Phase 3 clinical trials in the second half of 2017, and, if successful, our plans to submit a New Drug Application (NDA) to the FDA in the first half of 2018;
- our expectations that patients completing the Phase 3 clinical trials in Ménière’s disease will enroll in an open-label clinical safety trial and receive two quarterly doses of OTO-104;
- our expectations regarding the clinical development of OTO-311, including but not limited to our plans to initiate a Phase 2 clinical trial in tinnitus patients in the second half of 2017;
- our expectations regarding our future development of our product candidates for additional indications;
- the timing or likelihood of regulatory filings and approvals;
- our expectations regarding the future development of other product candidates;
- our expectations regarding the multiple-dose clinical safety requirement for U.S. regulatory approval of OTO-104 in the United States in patients with Ménière’s;
- the potential for commercialization of our product candidates, if approved;
- our expectations and statements regarding the pricing, market size, opportunity and growth potential for OTIPRIO and OTO-104 and OTO-311, if approved for commercial use;
- our expectations and statements regarding the adoption and use of OTIPRIO and OTO-104 and OTO-311, if approved, by ear, nose and throat physicians (ENTs);
- our expectations regarding potential coverage and reimbursement relating to OTIPRIO, and OTO-104 and OTO-311, if approved, or any other approved product candidates;
- our plans regarding the use of contract manufacturers for the production of our product candidates for clinical trials and, if approved, commercial use;
- our plans and ability to effectively expand and manage our own sales and marketing capabilities, or seek and establish collaborative partners, to commercialize our products;
- our expectations regarding the financial and other impact of our sales territory realignment;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- the implementation of our business model, strategic plans for our business, products and technology;
- the initiation, timing, progress and results of future preclinical studies and clinical trials;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our products and technology;
- estimates of our expenses, future revenue, capital requirements and our needs for additional financing;
- our financial performance;
- accounting principles, policies and estimates;
- developments and projections relating to our competitors and our industry; and
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including but not limited to: our limited operating history and our expectation that it we incur significant losses for the foreseeable future; our ability to obtain additional financing; our dependence on the commercial success of OTIPRIO and the regulatory success and advancement of additional product candidates, such as OTO-104 and OTO-311, and label expansion indications for OTIPRIO; the uncertainties inherent in the clinical drug development process, including, without limitation, our ability to adequately demonstrate the safety and efficacy of our product candidates, the preclinical and clinical results for our product candidates, which may not support further development, and challenges related to patient enrollment in clinical trials; our ability to obtain regulatory approval for our product candidates; side effects or adverse events associated with our product candidates; competition in the biopharmaceutical industry; our dependence on third parties to conduct preclinical studies and clinical trials; the timing and outcome of hospital pharmacy and therapeutics reviews and other facility reviews; the impact of coverage and reimbursement decisions by third-party payors on the pricing and market acceptance of OTIPRIO; our dependence on third parties for the manufacture of OTIPRIO and product candidates; our dependence on a small number of suppliers for raw materials; our ability to protect our intellectual property related to OTIPRIO and our product candidates in the United States and throughout the world; expectations regarding potential market size, opportunity and growth; our ability to manage operating expenses; implementation of our business model and strategic plans for our business, products and technology; and other risks. Information regarding the foregoing and additional risks are described in the section entitled “Risk Factors” and elsewhere in this Annual Report on Form 10-K. Moreover, we operate in a very competitive and rapidly changing environment, and new risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this Annual Report on Form 10-K may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. Moreover, neither we nor any other person assumes responsibility for the accuracy and completeness of the forward-looking statements. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this Annual Report on Form 10-K to conform these statements to actual results or to changes in our expectations, except as required by law.

You should read this Annual Report on Form 10-K and the documents that we reference in this Annual Report on Form 10-K and have filed with the SEC as exhibits to this Annual Report on Form 10-K with the understanding that our actual future results, levels of activity, performance, and events and circumstances may be materially different from what we expect.

PART I

Item 1. BUSINESS

Overview

Otonomy is a biopharmaceutical company focused on the development and commercialization of innovative therapeutics for diseases and disorders of the ear. OTIPRIOâ (ciprofloxacin otic suspension) is approved in the United States for use during tympanostomy tube placement (TTP) surgery in pediatric patients, has achieved positive pivotal trial results in patients with acute otitis externa (AOE), and has completed a successful Phase 2 trial in patients with acute otitis media with tubes (AOMT). OTO-104 is a steroid in development for the treatment of Ménière's disease and other severe balance and hearing disorders. Two Phase 3 trials in Ménière's disease patients are underway with results expected during the second half of 2017, and a Phase 2 trial has been initiated in patients at risk for cisplatin-induced hearing loss. OTO-311 is a N-Methyl-D-Aspartate (NMDA) receptor antagonist for the treatment of tinnitus that has completed a Phase 1 clinical safety trial with a Phase 2 trial expected to be initiated in the second half of 2017. 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:

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 was available for commercial purchase beginning in March 2016. OTIPRIO 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 are commercializing OTIPRIO using an internal sales force that calls on physicians who perform TTP surgeries and the facilities where these procedures are performed.

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 are also evaluating OTIPRIO for potential label expansion in several indications beginning with AOE, also known as swimmer's ear. We have completed a Phase 3 clinical trial in 262 pediatric and adult patients with AOE that met the primary endpoint by showing a statistically significant increase in clinical cure rate for OTIPRIO compared to sham (no treatment) at Day 8 ($p<0.001$). OTIPRIO also demonstrated a statistically significant superiority to sham in clinical cure rate at all other time points assessed including Day 4 ($p<0.021$), Day 15 ($p<0.001$) and Day 29 ($p<0.001$), and was well-tolerated. Based on these positive results, Otonomy expects to submit a supplemental New Drug Application (sNDA) with the FDA in the first half of 2017.

A second potential label expansion indication for OTIPRIO is AOMT. We have completed a Phase 2 clinical trial in 95 pediatric patients that demonstrated higher and statistically significant ($p<0.05$) clinical cure rates for a single administration of OTIPRIO (either 6 mg or 12 mg) compared to sham (no treatment), and showed that OTIPRIO was well-tolerated. We believe this trial supports the advancement of OTIPRIO into Phase 3 in AOMT and intend to discuss the requirements for such a program with the FDA in the first half of 2017.

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

As of December 31, 2016, net sales of OTIPRIO totaled $0.7 million. We sell OTIPRIO to specialty wholesale distributor customers. Three of our major customers – ASD Specialty Healthcare, Inc., Cardinal Health 108 LLC and McKesson Plasma and Biologics LLC – each accounted for 10% or more of our 2016 annual revenue.

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 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 are conducting two parallel Phase 3

clinical trials in Ménière's disease using DVD during Month 3 as the primary endpoint. The AVERTS-1 trial was initiated in the United States in the fourth quarter of 2015 and the AVERTS-2 trial was initiated in Europe during the first quarter of 2016. Each trial is a 16-week, prospective, randomized, double-blind, placebo-controlled trial that is expected to enroll approximately 160 patients with unilateral Ménière's disease. Results from the Phase 3 trials are expected in the second half of 2017. If successful, we expect to submit a New Drug Application (NDA) for OTO-104 to the FDA in the first half of 2018. 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. In January 2017, we announced the enrollment of the first patients in a Phase 2 clinical trial evaluating OTO-104 for the prevention of hearing loss in cancer patients undergoing chemotherapy with platinum-based agents. This multicenter, randomized trial is designed to assess the feasibility, safety and efficacy of OTO-104 given by intratympanic administration in subjects at risk for ototoxicity from cisplatin chemotherapy. Up to 60 subjects will receive an administration of OTO-104 in one ear prior to each of the first three cisplatin treatment cycles with hearing assessed throughout the trial and following the last chemotherapy treatment cycle.

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. Several clinical trials have demonstrated reductions in the severity of tinnitus and improvement in the functional status of patients following treatment with an NMDA receptor antagonist. We expect that the results of these 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. We have successfully completed a Phase 1 clinical safety trial in normal healthy volunteers and expect to initiate a Phase 2 clinical trial in tinnitus patients in the second half of 2017.

Program 4: Treatment for Sensorineural Hearing Loss

We have acquired the rights to multiple product candidates for our fourth development program, which will target sensorinerual hearing loss including age-related hearing loss, also known as presbycusis. According to the National Institute on Deafness and Other Communication Disorders, there are nearly 40 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 88 issued patents and allowed patent applications and at least 115 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.

Competition

The biopharmaceutical market is highly competitive. Successful competitors in the biopharmaceutical market must have the ability to effectively discover, develop, test and obtain regulatory approvals for products, as well as the ability to effectively commercialize, market and promote approved products, including communicating the effectiveness, safety and value of products to actual and prospective customers and medical staff. Numerous companies are engaged in the development, manufacture and marketing of biopharmaceutical products competitive with those that we are developing. Our potential competitors may have substantially greater manufacturing, financial, research and development, personnel and marketing resources than we have. Our competitors may also have more experience and expertise in obtaining marketing approvals from the FDA and other regulatory authorities. In addition to product development, testing, approval and promotion, other competitive factors in the biopharmaceutical industry include industry consolidation, product quality and price, product technology, reputation, customer service and access to technical information. As a result, our competitors may be able to develop competing or superior technologies and processes, and

compete more aggressively and sustain that competition over a longer period of time than we could. Our technologies and products may be rendered obsolete or uneconomical by technological advances or entirely different approaches developed by one or more of our competitors. As more companies develop new intellectual property in our market, the possibility of a competitor acquiring patent or other rights that may limit our products or potential products increases, which could lead to litigation.

Any product candidates that we successfully develop and commercialize will compete with existing treatments, including unapproved and off-label drug alternatives that are currently utilized by physicians to treat the indications for which we seek approval, as well as new treatments that may become available in the future.

OTIPRIO

Antibiotic ear drops are currently the primary treatment option for use during TTP surgery even though no ear drop product has been approved by the FDA for this indication. Multiple ear drops are approved and marketed for use in treating patients with AOE and AOMT. Marketed antibiotic ear drops include CIPRODEXâ Otic from Alcon, a Novartis company, and Otovelâ from Arbor Pharmaceuticals, LLC. The key competitive factors affecting the success of OTIPRIO are likely to be its efficacy, safety, tolerability, dosing regimen, route of administration, convenience and price, and the availability of coverage and adequate reimbursement from government and other third-party payors.

OTO-104

There are no drugs currently approved by the FDA for the treatment of Ménière's disease. Current treatments commonly used for Ménière's disease include observance of a low-salt diet and off-label use of diuretics, oral steroids, and repeat IT injections of steroid solution. Patients who are unresponsive to treatment may resort to surgical or chemical ablation, which can cause irreversible hearing loss. We are aware that Synphora AB is conducting a Phase 2/3 clinical trial with a formulation of latanoprost administered via single or repeat IT injections, Sound Pharmaceuticals has initiated a Phase 1b clinical trial with SP-1005 which is an oral formulation of ebselen, and Auris Medical Holding AG has indicated it intends to develop AM-125 for the treatment of vertigo disorders including Ménière's disease.

OTO-311

There are no drugs currently approved by the FDA for the treatment of tinnitus. Current treatments for tinnitus include the use of audio masking devices, such as white noise machines, hearing aids, cognitive behavioral therapy, and the off-label administration of antidepressants, anti-anxiety medications, and steroids. We are aware of other companies developing potential pharmaceutical treatments for tinnitus, including Auris Medical Holding AG, which is conducting a Phase 3 clinical program evaluating repeat IT injections of Keyzilenâ (formerly AM-101) in patients with acute and post-acute inner ear tinnitus. The first Phase 3 trial failed to achieve the primary endpoint and a second Phase 3 trial is ongoing. We are also aware that Autifony Therapeutics terminated a Phase 2 trial for AUT00063 in tinnitus patients following a planned interim analysis, Merz Pharmaceuticals GmbH suspended development of oral neramexane for chronic tinnitus while its partner in Japan, Kyorin Pharmaceutical Co., continues with a Phase 2 clinical trial for tinnitus, and Novartis AG completed a Phase 2 clinical trial for chronic tinnitus.

Sales and Marketing

We are commercializing OTIPRIO and plan to commercialize OTO-104, OTO-311 and any other approved products in the United States with our own focused, specialized sales force. Outside of the United States, we plan to evaluate whether to commercialize our products on our own or in collaboration with partners.

Third-Party Payor Coverage and Reimbursement

Sales of pharmaceutical products depend in significant part on the availability of coverage and adequate reimbursement by third-party payors, such as state and federal governments, including Medicare and Medicaid, and commercial insurers. Decisions regarding the extent of coverage and amount of reimbursement to be provided for our products will most likely be made on a plan-by-plan basis.

OTIPRIO

We expect OTIPRIO to be reimbursed as a physician-administered drug in the United States. We have set the Wholesale Acquisition Cost for OTIPRIO at $283.20 per vial which is sufficient for treating both ears of a single patient. This pricing represents a premium to CIPRODEX Otic, the leading branded ear drop product, which has a current reported Wholesale Acquisition Cost of

approximately $200 per unit which is sufficient for a full course of treatment. In order for physicians to use OTIPRIO, we will need to have the product available in hospital outpatient facilities and ambulatory surgery centers (ASCs) where the majority of pediatric TTP procedures are performed.

The stocking of OTIPRIO in hospital outpatient facilities and ASCs typically requires approval from hospital pharmacy and therapeutic committees and ASC administrators, respectively. The review by hospital pharmacy and therapeutic committees typically considers the product profile, clinical safety and efficacy results, current treatments used for the indication, level of interest/advocacy by the physician user base, and impact on facility economics. This process can require up to a year to complete and approval is uncertain. The time and requirements for approval by ASC administrators typically varies by center and depends on a number of factors including level of interest / advocacy by the physician user base and impact to the facility economics.

As an FDA-approved, physician-administered medication, we applied to the Centers for Medicare and Medicaid Services (CMS) for a unique C Code and J Code for OTIPRIO. The C Code was assigned by CMS and became effective as of July 1, 2016. Use of this code could provide for pass-through payment of OTIPRIO when used in the outpatient hospital and ASC setting for a transitional period of two to three years. In November 2016, we announced that CMS had established a unique J Code for OTIPRIO which became effective as of January 1, 2017. The J Code replaces the C code while retaining transitional pass-through payment status. The J Code could also provide for reimbursement of OTIPRIO when used in the physician office setting. If the J Code is accepted for separate payment by payors then OTIPRIO could be reimbursed based on the product’s average selling price. The OTIPRIO commercial launch plan includes a comprehensive set of programs to support the value proposition of OTIPRIO with facility administrators and payors.

OTO-104 and OTO-311

If approved by the FDA, we intend to apply to CMS for unique J Codes for both OTO-104 and OTO-311 to support reimbursement in the physician office setting. If a J Code is granted and accepted by payors then each product is expected to be reimbursed according to its average selling price and in addition to the fee the physician receives for performing the IT injection procedure itself. We currently project that the average selling price for both OTO-104 and OTO-311 will be in excess of $1,000 per treatment.

Manufacturing

We currently contract with third parties for the manufacture, testing and storage of our product and product candidates and intend to continue to do so in the future. We do not own and have no plans to build our own clinical or commercial manufacturing capabilities. The use of contracted manufacturing is relatively cost-efficient and has eliminated the need for our direct investment in manufacturing facilities. Because we rely on contract manufacturers, we employ personnel with extensive technical, manufacturing, analytical and quality experience to oversee contract manufacturing and testing activities, and to compile manufacturing and quality information for our regulatory submissions.

Manufacturing is subject to extensive regulations that impose various procedural and documentation requirements, and which govern record keeping, manufacturing processes and controls, personnel, quality control and quality assurance, among others. Our systems and our contractors are required to be in compliance with these regulations, and this is assessed regularly through monitoring of performance and a formal audit program. To date, our third-party manufacturers have met our manufacturing requirements for clinical trials and our third-party manufacturer for OTIPRIO successfully passed a pre-approval inspection conducted by the FDA. We expect third-party manufacturers to be capable of providing sufficient quantities of our product and product candidates to meet anticipated commercial demands. We believe that there are alternate sources of raw material supply and finished goods manufacturing that can

satisfy our requirements, although we cannot be certain that transitioning to such vendors, if necessary, would not result in significant delay or material additional costs.

Poloxamer 407

The basis for the formulation of our product and current product candidates is P407, a thermosensitive polymer. We currently purchase P407 from a single supplier on a purchase-order basis under a supply agreement. Although P407 is available from other sources, changing suppliers could disrupt our supply chain. We believe that we can effectively manage the risk of supply chain disruption by purchasing and storing quantities of P407 sufficient for our clinical and commercial requirements.

OTIPRIO

OTIPRIO is a suspension containing the antibiotic ciprofloxacin and P407. The raw materials needed for the manufacture of OTIPRIO are commercially available from multiple sources. We have qualified two sources of ciprofloxacin and have a supply

agreement in place with one of the vendors. We currently use a single third-party contract manufacturer, Siegfried Irvine, located in Irvine, California, to produce OTIPRIO, and we believe this manufacturer can satisfy our commercial requirements as specified under a commercial supply agreement executed with this manufacturer.

OTO-104

OTO-104 is a suspension containing the steroid dexamethasone and P407. We currently purchase dexamethasone from a single supplier on a purchase-order basis and we do not have a long-term supply agreement. Although dexamethasone is commercially available from other sources, we do not anticipate needing an alternative supplier. We believe that we can effectively manage the risk of supply chain disruption by purchasing and storing quantities of dexamethasone sufficient for our clinical, and, if OTO-104 is approved for marketing by the applicable regulatory authorities, our commercial requirements. We currently use two third-party contract manufacturers to produce OTO-104 that we believe can satisfy our clinical requirements. We are currently evaluating our supply chain for the commercial manufacture of OTO-104.

OTO-311

OTO-311 is a suspension containing gacyclidine and P407. We currently purchase gacyclidine from a single supplier on a purchase-order basis and we do not have a long-term supply agreement. We currently use one third-party contract manufacturer to produce OTO-311 that we believe can satisfy our clinical requirements.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary protection for our product, product candidates, novel discoveries, product development technologies and other know-how, to operate without infringing on the proprietary rights of others and to prevent others from infringing our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trademarks, trade secrets, know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position.

As for the product candidates we develop and plan to commercialize, as a normal course of business, we intend to pursue composition and therapeutic use patents, as well as novel indications for our product candidates. We also seek patent protection with respect to novel discoveries, including new active agent, delivery vehicle and delivery target applications. We have also pursued patents with respect to our proprietary manufacturing processes. We have sought and plan to continue to seek patent protection, either alone or jointly with our collaborators, as our collaboration agreements may dictate.

It is possible that our current patents, or patents which we may later acquire, may be successfully challenged or invalidated in whole or in part. Nevertheless, we are not aware of any issued patents that we believe would prevent us from marketing OTIPRIO or our product candidates. It is also possible that we may not obtain issued patents from our pending patent applications or other inventions we seek to protect. Due to uncertainties inherent in prosecuting patent applications, patent applications are sometimes rejected and we subsequently abandon them. It is also possible that we may develop proprietary products or technologies in the future that are not patentable or that the patents of others will limit or altogether preclude our ability to do business. In addition, any patent issued to us may provide us with little or no competitive advantage, in which case we may abandon such patent or license it to another entity. For more information, please see “Risk Factors—Risks Related to Our Intellectual Property.”

Our patent estate includes patents and applications with claims directed to OTIPRIO, and our OTO-104 and OTO-311 product candidates. Our patent estate also provides patents and applications with claims directed to a broad range of other active agents as potential future product candidates that are delivered through our proprietary technology. Our patent estate, on a worldwide basis, includes approximately 88 issued patents and allowed patent applications, and at least 115 pending patent applications with claims relating to our OTIPRIO, OTO-104, OTO-311, future product candidates, manufacturing processes and alternative otic delivery technologies.

For OTIPRIO, we co-own a patent family with The Regents of the University of California (UC) that is directed to the composition and therapeutic use of OTIPRIO. Through an exclusive license agreement, we have acquired UC's rights in this patent family. This family includes four issued U.S. patents and three pending U.S. applications. The latest expiry date of the U.S. patents, without extensions, is April 2030, and the first three issued U.S. patents have been Orange Book (OB) listed. The fourth issued patent is expected to be OB listable for OTIPRIO's expanded indication (AOE) if approved by FDA. Any future U.S. patents issuing from the related applications and directed to OTIPRIO are also expected to be OB listable. This family also includes issued patents or allowed applications in Australia, Canada, Europe, Israel, Japan, Korea, Mexico, Philippines, Russia, Singapore, South Africa and

Taiwan; and pending applications in Argentina, Brazil, China, India, Jordan, Pakistan, Thailand, Uruguay and Venezuela. Divisional patent applications have been filed in select countries of this family. In addition, we solely own a patent family directed to certain therapeutic uses of OTIPRIO, which includes an issued U.S. patent that has been submitted for OB listing and can extend patent protection of OTIPRIO to August 2034. Furthermore, we solely own a patent family directed to OTIPRIO and its manufacturing methods, which includes an issued U.S. patent that has been OB listed and extends patent protection of OTIPRIO to July 2035. Finally, we solely own a patent family directed to the packaged OTIPRIO product, and have filed two solely owned U.S. provisional applications directed to certain therapeutic use of OTIPRIO.

For OTO-104, we co-own a patent family with UC directed to the composition and therapeutic use of OTO-104. Through an exclusive license agreement, we have acquired UC's rights in this patent family. This family includes six issued U.S. patents and one pending U.S. application. The latest expiry date of the U.S. patents, without extensions, is September 2029, and these patents and any future U.S. patent issuing from the related applications are expected to be OB listable. This family also includes issued patents or allowed applications in Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan, Korea, Mexico, Peru, Philippines, Russia, Singapore, South Africa, Taiwan and UK; and pending applications in Argentina, Brazil, Chile, Indonesia, Jordan, Malaysia, Pakistan, Thailand, Uruguay, Venezuela and Vietnam. Divisional patent applications have been filed in select countries for this family. In addition, we solely own a patent family directed to additional therapeutic uses of OTO-104, including prevention of chemotherapeutic drug-induced ototoxicity. Finally, we solely own an issued U.S. patent directed to manufacturing methods of OTO-104. The expiry date of this U.S. patent, without extensions, is April 2030.

For OTO-311, we co-own two patent families with UC directed to the composition and therapeutic use of OTO-311. Through an exclusive license agreement, we have acquired UC's rights in both patent families. These families include three issued U.S. patents and two pending U.S. applications. The latest expiry date of the U.S. patent, without extensions, is April 2031, and these patents and any future U.S. patent issuing from this application are expected to be OB listable. These families also include issued patents or allowed applications in Australia, Canada, Chile, China, Japan, Korea, Mexico, Russia, South Africa, Taiwan and UK; and pending applications in Argentina, Brazil, Europe, India, Israel, Jordan, Pakistan, Thailand, Uruguay and Venezuela. Divisional patent applications have been filed in select countries for those families. In addition, we have licensed from Durect a patent family directed to the therapeutic use of OTO-311. This family includes one issued U.S. patent and one issued Japanese patent. The expiry date of the U.S. patent, without extension, is June 2024, and the patent is expected to be OB listable.

For Program 4, we have acquired rights in a patent family that are directed to certain product candidates. We have also filed three families of patent applications, which we co-own, that are directed to certain product candidates.

For our future product candidates, we co-own eight other patent families with UC directed to a broad range of other active agents, including but not limited to, anti-TNF agents, auris pressure modulators, CNS modulators, cytotoxic agents, anti-apoptotic agents, bone-remodeling modulators, free radical modulators and ion channel modulators. As above, we have acquired, though an exclusive license, UC's rights in those co-owned families. Furthermore, to strengthen our protection against potential design-around, we solely own a patent family directed to alternative formulations. Finally, we have acquired from IncuMed LLC, an affiliate of the NeuroSystec Corporation, patent families directed to formulations or devices that deliver active agents, such as the active agent of OTO-311, into the ear for treatment of otic diseases through alternative delivery technologies. We will continue to pursue additional patent protection as well as take appropriate measures to obtain and maintain proprietary protection for our innovative technologies.

Individual patents extend for varying periods depending on the date of filing of the patent application or the date of patent issuance and the legal term of patents in the countries in which they are obtained. Generally, patents issued for regularly filed applications in the United States are effective for 20 years from the earliest effective filing date. In

addition, in certain instances, a patent term can be extended to recapture a portion of the U.S. Patent and Trademark Office (USPTO) delay in issuing the patent as well as a portion of the term effectively lost as a result of the FDA regulatory review period. However, as to the FDA component, the restoration period cannot be longer than five years and the total patent term including the restoration period must not exceed 14 years following FDA approval. The duration of foreign patents varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective filing date. In addition to the patents and allowed applications described in the preceding paragraphs, our pending patent applications related to our product candidates, if issued, are expected to expire on dates ranging from 2029 to 2032. However, the actual protection afforded by a patent varies on a product by product basis, from country to country and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent.

In addition to patents, we have obtained trademark registration for “OTIPRIO” in the United States, Europe, Japan, Korea, and New Zealand, and have pending trademark application for “OTIPRIO” in Australia, Canada, and China. Furthermore, we rely upon trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our commercial partners, collaborators, employees and consultants and invention assignment agreements with our employees. We also have confidentiality agreements or invention

assignment agreements with our commercial partners and selected consultants. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed through a relationship with a third party. These agreements may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our commercial partners, collaborators, employees and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For more information, please see "Risk Factors—Risks Related to Our Intellectual Property."

Our commercial success will also depend in part on not infringing upon the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, or our drugs or processes, obtain licenses or cease certain activities. Our breach of any license agreements or failure to obtain a license to proprietary rights that we may require to develop or commercialize our future products may have a material adverse impact on us. If third parties prepare and file patent applications in the United States that also claim technology to which we have rights, we may have to participate in interference proceedings in the USPTO, to determine priority of invention. Although it is not expected to be relevant to our product or any of our product candidates, on April 17, 2015, we filed a request for interference between one of our U.S. pending applications and a U.S. pending application that appears to be controlled by Auris Medical AG (Auris). On July 20, 2015, we received notice from the USPTO that the Patent Trial and Appeal Board (PTAB) declared an interference between our pending application and the Auris patent (issued as U.S. Patent No. 9,066,865 on June 30, 2015). On January 26, 2017, the PTAB determined that all of Otonomy's patent claims and all but one of the Auris' patent claims are not patentable. In addition, the PTAB determined that the written description supporting Auris' single claim is as of Auris' filing date of 2014 rather than the 2005 dated argued by Auris. This interference decision does not involve issued U.S. patents covering our product or product candidates. For more information, please see "Risk Factors—Risks Related to Our Intellectual Property."

License and Other Agreements

The Regents of the University of California

In November 2008, we entered into an exclusive license agreement with UC that was subsequently amended in January 2010, June 2010, and November 2012. Under the license agreement, UC granted us an exclusive license under UC's rights to patents and applications that are co-developed and co-owned with us (see above regarding our patent estate) for the treatment of human otic diseases. As such, we have acquired the entire commercial rights in those patents and applications that cover OTIPRIO and our current and future product candidates. Under the agreement, UC reserved the right to use the patents and applications for its and other nonprofit institutions' research and educational purposes.

Under our agreement with UC, we are obligated to diligently proceed with the development, manufacture and commercialization of licensed products. If we do not satisfy our diligence obligations, UC may either terminate the agreement or convert our license to a non-exclusive license. In addition, we are responsible for diligently prosecuting and maintaining the licensed patents, at our own expense; provided that if we decide to abandon a licensed patent, UC may elect to continue prosecution and maintenance of such patent at its own expense. UC has the first right to prosecute and control any action for infringement of the patents licensed to us under our agreement with UC; provided that if UC does not initiate an enforcement action against a potential infringer within the time limits specified in the agreement, we have the right to do so ourselves.

Our financial obligations under the license agreement include annual license maintenance payments until we commercialize the first product covered under the license agreement, development milestone payments of up to $2.7

million per licensed product, of which $1.9 million has been paid for OTIPRIO, $0.8 million has been paid for OTO-104, and $0.1 million has been paid for OTO-311 (but such milestone payments are reduced by 75% for any orphan indication product), and a low single-digit royalty on net sales by us or our affiliates of licensed products. In addition, for each sublicense we grant we are obligated to pay UC a fixed percentage of all royalties as well as a sliding scale percentage of non-royalty sublicense fees received by us under such sublicense, with such percentage depending on the licensed product's stage of development when sublicensed to such third party. We have the right to offset a certain amount of third-party royalties, milestone fees or sublicense fees against the foregoing financial obligations, provided such third-party royalties or fees are paid by us in consideration for intellectual property rights necessary to commercialize a licensed product.

Unless earlier terminated, the agreement will continue in effect until expiration of the longest lived patent licensed to us thereunder. UC may terminate the license agreement for our uncured breach, or if a claim challenging the validity of the licensed patents is filed by or on behalf of us. We have the right to terminate this agreement for any reason at any time upon prior notice to UC. The termination of our license agreement with UC may affect a portion of our patent portfolio for OTIPRIO, OTO-104, and OTO-311. For more information, please see "Risk Factors—Risks Related to our Intellectual Property."

DURECT Corporation

In April 2013, we entered into an exclusive license agreement with Durect as a part of an asset transfer agreement between us and IncuMed LLC, an affiliate of the NeuroSystec Corporation. Under this license agreement, Durect granted us an exclusive (even as to Durect), worldwide, royalty-bearing license under Durect's rights to certain patents and applications that cover our OTO-311 product candidate, as well as certain related know-how. Included within the rights licensed from Durect is a sublicense from the Institut National de la Sante et de la Recherche Medicale (INSERM) with respect to INSERM's ownership interest in certain patents and patent applications owned jointly by INSERM and Durect.

We are obligated to use commercially reasonable efforts to develop and commercialize licensed products containing the active ingredient gacyclidine, and in the event we do not satisfy this obligation following an opportunity to cure, Durect may elect to either terminate the agreement or convert our license to a non-exclusive license. In addition, we are responsible for prosecuting and maintaining the licensed patents, at our own expense; provided that if we decide to abandon a licensed patent, Durect may elect to continue prosecution and maintenance of such patent at its own expense. We have the first right, but not obligation, to prosecute and control any action for infringement of the patents licensed to us under our agreement with Durect.

We are also subject to certain financial obligations under the license agreement. We are obligated to make one-time development milestone payments of up to $2.3 million for the first licensed product. Upon commercializing a licensed product, we are obligated to pay Durect tiered low single-digit royalties on annual net sales by us or our affiliates or sublicensees of the licensed products, and we have the right to offset a certain amount of third-party license fees or royalties against such royalty payments to Durect, provided such third-party fees or royalties are paid by us in connection with patent rights necessary to sell a licensed product containing the active ingredient gacyclidine. In addition, each sublicense we grant to a third party is subject to payment to Durect of a low double-digit percentage of all non-royalty payments we receive under such sublicense. Additionally, we are also obligated to pay INSERM, on behalf of Durect, a low single-digit royalty payment on net sales by us or our affiliates or sublicensees upon commercialization of the licensed product. The foregoing royalty payment obligation to Durect would continue on a product-by-product and country-by-country basis until expiration or determination of invalidity of the last valid claim within the licensed patents that cover the licensed product, and the payment obligation to INSERM would continue so long as Durect's license from INSERM remains in effect.

Unless earlier terminated, the agreement will continue in effect until expiration of all our royalty payment obligations thereunder. Durect may terminate the license agreement for our uncured material breach, and either party may terminate the agreement upon written notice in the event of insolvency or bankruptcy of the other party. We have the right to terminate this agreement for any reason at any time upon prior notice to Durect. The termination of our license agreement with Durect would affect a portion of our patent portfolio for OTO-311. For more information, please see "Risk Factors—Risks Related to our Intellectual Property."

Asset Transfer Agreement

In April 2013, we entered into an asset transfer agreement with IncuMed, LLC, an affiliate of NeuroSystec Corporation, pursuant to which we acquired assets and patent rights related to gacyclidine. Pursuant to the asset transfer agreement, we made a one-time payment of $0.2 million and we are obligated to make certain one-time milestone payments in connection with the development and commercialization of products containing the active ingredient gacyclidine, up to a maximum of $5.3 million.

Government Regulation

Government authorities in the United States (at the federal, state and local level) and in other countries extensively regulate, among other things, the research, development, testing, quality control, manufacture, packaging, storage, recordkeeping, approval, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources. Our product candidates must be approved by the FDA before they may be legally marketed in the United States and by the appropriate foreign regulatory agency before they may be legally marketed in foreign countries. Generally, our activities in other countries will be subject to regulation that is similar in nature and scope as that imposed in the United States, although there can be important differences. Additionally, some significant aspects of regulation in Europe are addressed in a centralized way, but country-specific regulation remains essential in many respects.

U.S. Drug Approval Process

In the United States, the FDA regulates drugs under the federal Food, Drug, and Cosmetic Act (FDCA) and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and

foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's current good laboratory practice (cGLP) regulations;
- submission to the FDA of an IND which must become effective before clinical trials may begin;
- approval by an independent institutional review board (IRB) at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled clinical trials in accordance with current good clinical practices (cGCP) to establish the safety and efficacy of the proposed drug or biological product for each indication;
- submission to the FDA of an NDA;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and
- FDA review and approval of the NDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess its potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to patients under the supervision of qualified investigators in accordance with cGCP requirements, which include the requirement that all research patients provide their informed consent (assent, if applicable) in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety and the effectiveness 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. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health (NIH) for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- Phase 1 : The drug is initially introduced into healthy human patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness.
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Phase 2 : The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

- Phase 3 : The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA may impose a partial or full clinical hold or the sponsor may suspend or terminate a clinical trial or development at any time on various grounds, including a finding that the research patients are being exposed to an unacceptable health risk.

Development, or the aspects of development, that are subject to clinical hold may not continue until the sponsor has satisfied FDA requirements for information and has been notified that the hold is being removed. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

The NDA Approval Process

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. Under the Prescription Drug User Fee Act (PDUFA) guidelines that are currently in effect, the FDA has a goal of ten months from the date of the FDA's filing of a standard non-priority NDA to review and act on the submission.

The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity. The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured, which is not under the control of the product sponsor. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with cGCP.

The FDA also may require submission of a risk evaluation and mitigation strategy (REMS) plan to mitigate any identified or suspected serious risks. The REMS plan could include medication guides, physician communication plans, assessment plans and elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools.

The testing and approval process requires substantial time, effort and financial resources, and each may take several years to complete. Data obtained from clinical activities are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all.

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new products that meet certain criteria. Specifically, new products are eligible for Fast Track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. Unique to a Fast Track product, the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA. Our Fast Track Designation for OTO-104 may not result in faster development or approval, if at all.

If the FDA's evaluation of the NDA and inspection of the manufacturing facilities are favorable, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the

application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

The Section 505(b)(2) NDA

For modifications to products previously approved by the FDA, an applicant may file an NDA under Section 505(b)(2) of the FDCA. This section permits the submission of an NDA where some or all of the data required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. Under this section, an applicant may rely on the FDA's findings of safety and effectiveness in approval of another NDA or on studies published in the scientific literature. The applicant may be required to conduct additional studies or provide additional information to fully demonstrate the safety and effectiveness of its modifications to the approved product.

Upon approval of an NDA, the FDA lists the product in a publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," which is commonly known as the "Orange Book." FDA also lists in the Orange Book patents identified by the NDA applicant as claiming the drug or an approved method of using the drug. Any applicant who submits a Section 505(b)(2) NDA must certify to the FDA with regard to each relevant patent that either (1) no patent information has been submitted to the FDA; (2) the patent has expired; (3) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (4) the patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the Section 505(b)(2) NDA is submitted. The last certification is known as a Paragraph IV certification. A notice of Paragraph IV certification must be provided to each owner of the patent that is the subject of the certification and to the holder of the approved NDA to which the Section 505(b)(2) NDA refers. If the NDA holder submits the patent information to the FDA prior to submission of the Section 505(b)(2) application and the NDA holder or patent owner(s) sues the Section 505(b)(2) applicant for infringement within 45 days of its receipt of the certification notice, the FDA is prevented from approving that Section 505(b)(2) application until the earlier of 30 months from the receipt of the notice of the Paragraph IV certification, the expiration of the patent or such shorter or longer period as may be ordered by a court. This prohibition is generally referred to as the 30-month stay. A Section 505(b)(2) applicant that is sued for infringement may file a counterclaim to challenge the listing of the patent or information submitted to FDA about the patent. If we file a Paragraph IV certification with any Section 505(b)(2) application, we cannot assure you that our application will not be significantly delayed as a result of costly patent litigation.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior

FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies to determine compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend significant time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label, although doctors may prescribe drugs for off-label purposes.

The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act (PDMA) which regulates the distribution of drug and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states.

Hatch-Waxman Exclusivity

Market and data exclusivity provisions under the Federal Food, Drug, and Cosmetic Act (FFDCA) can delay the submission or the approval of certain applications for competing products. The FFDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an Abbreviated New Drug Application (ANDA) or a Section 505(b)(2) NDA submitted by another company that references the previously approved drug. However, an ANDA or Section 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FFDCA also provides three years of marketing exclusivity for an NDA, Section 505(b)(2) NDA or supplement to an existing NDA or Section 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant, are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or Section 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

New Legislation and Regulations

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

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we may obtain regulatory approval. Sales of any of our product candidates, if approved, will depend, in part, on the extent to which the costs of the

products will be covered by third-party payors, including government health programs such as Medicare and Medicaid, commercial health insurers and managed care organizations. The process for determining whether a third-party payor will provide coverage for a drug product typically is separate from the process for setting the price of a drug product or for establishing the reimbursement rate that a payor will pay for the drug product once coverage is approved. Third-party payors may limit coverage to specific drug products on an approved list, also known as a formulary, which might not include all of the approved drugs for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Whether or not we conduct such studies, our product candidates may not be considered medically necessary or cost-effective. A third-party payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage, and adequate reimbursement, for the product. Third-party reimbursement may not be sufficient to enable us to maintain price levels high enough to realize an appropriate return on our investment in product development.

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of drugs have been a focus in this effort. Third-party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost-effectiveness of drug products and medical services and questioning safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after FDA approval or, if they do, the level of payment may not be sufficient to allow us to sell our products at a profit. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. Adoption of such controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals such as our drug product candidates and could adversely affect our net revenue and results.

Pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. For example, the EU provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. EU member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements for any of our products.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on drug pricing. Coverage policies, third-party reimbursement rates and drug pricing regulation may change at any time. In particular, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation

Act of 2010, which we collectively refer to as the Affordable Care Act (ACA) contains provisions that have the potential to substantially change healthcare delivery and financing, including impacting the profitability of drugs. For example, the Affordable Care Act revised the methodology by which rebates owed by manufacturers to the state and federal government for covered outpatient drugs under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate Program to utilization of covered drugs dispensed to individuals enrolled in Medicaid managed care organizations and subjected manufacturers to new annual fees and taxes for certain branded prescription drugs. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Healthcare Law and Regulation

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescribing of any product candidates for which we may obtain marketing approval. Our business operations and arrangements with investigators, healthcare professionals, consultants, third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws. These laws may constrain the business or financial arrangements and relationships through which we research, manufacture, market, promote, sell and distribute our products that obtain marketing approval. Restrictions under applicable federal and state healthcare laws, include, but are not limited to, the following:

- the federal healthcare Anti-Kickback Statute prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal false claims laws and civil monetary penalties law impose penalties and provide for civil whistleblower or qui tam actions against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment or approval that are false or fraudulent or making a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA) among other things, imposes criminal liability for knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes certain obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information without proper written authorization;
- the federal transparency requirements under the Affordable Care Act requires manufacturers of drugs, devices, biologicals and medical supplies to annually report to the Centers for Medicare & Medicaid Services (CMS) an agency within the U.S. Department of Health and Human Services (HHS) information related to payments and other transfers of value provided to physicians and teaching hospitals and certain ownership and investment interests held by physicians and their immediate family members; and
- analogous state and foreign laws, such as state anti-kickback and false claims laws, that may apply to our business operations, including our sales or marketing arrangements, and claims involving healthcare items or services reimbursed by governmental third-party payors, and in some instances, also such claims reimbursed by non-governmental third-party payors, including private insurers.

Similar to the federal law, certain states also have adopted marketing and/or transparency laws relevant to manufacturers, some of which are broader in scope. Other states impose restrictions on manufacturers marketing practices and require tracking and reporting of gifts, compensation, and other remuneration to healthcare professionals and entities. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws 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. 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 administrative, civil, and/or criminal penalties, damages, fines, disgorgement, individual imprisonment, exclusion from 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 is found to be not in compliance with applicable laws, they may be subject to administrative, civil, and/or criminal sanctions, including exclusions from government funded healthcare programs.

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. The cost of establishing a regulatory compliance system for numerous varying jurisdictions can be very significant. Whether or not we obtain FDA approval for a product, we would

need to obtain the necessary approvals by the comparable foreign regulatory authorities before we can commence clinical trials or marketing of the product in foreign countries and jurisdictions. Although many of the issues discussed above with respect to the United States apply similarly in the context of the EU, the approval process varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

The U.S. Foreign Corrupt Practices Act and Other Anti-Corruption Laws

We may be subject to a variety of domestic and foreign anti-corruption laws with respect to our regulatory compliance efforts and operations. The U.S. Foreign Corrupt Practices Act, commonly known as the FCPA, is a criminal statute that prohibits an individual or business from paying, offering, promising or authorizing the provision of money (such as a bribe or kickback) or anything else of value (such as an improper gift, hospitality, or favor), directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision in order to assist the individual or business in obtaining, retaining, or directing business or other advantages (such as favorable regulatory rulings). The FCPA also obligates companies with securities listed in the United States to comply with certain accounting provisions. Those provisions require a company such as ours to (i) maintain books and records that accurately and fairly reflect all transactions, expenses, and asset dispositions, and (ii) devise and maintain an adequate system of internal accounting controls sufficient to provide reasonable assurances that transactions are properly authorized, executed and recorded. The FCPA is subject to broad interpretation by the U.S. government. The past decade has seen a significant increase in enforcement activity. In addition to the FCPA, there are a number of other federal and state anti-corruption laws to which we may be subject, including, the U.S. domestic bribery statute contained in 18 USC § 201 (which prohibits bribing U.S. government officials) and the U.S. Travel Act (which in some instances addresses private-sector or commercial bribery both within and outside the United States). Also, a number of the countries in which we conduct activities have their own domestic and international anti-corruption laws, such as the UK Bribery Act 2010. There have been cases where companies have faced multi-jurisdictional liability under the FCPA and the anti-corruption laws of other countries for the same illegal act.

We can be held liable under the FCPA and other anti-corruption laws for the illegal activities of our employees, representatives, contractors, partners, agents, subsidiaries, or affiliates, even if we did not explicitly authorize such activity. Although we will seek to comply with anti-corruption laws, there can be no assurance that all of our employees, representatives, contractors, partners, agents, subsidiaries or affiliates will comply with these laws at all times. Noncompliance with these laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain governments or other persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. In addition, our directors, officers, employees, and other representatives who engage in violations of the FCPA and certain other anti-corruption statutes may face imprisonment, fines, and penalties. If any subpoenas or investigations are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition