INSMED Inc
Form 10-K
February 27, 2015

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ý ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2014

OR

o 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 0-30739

INSMED INCORPORATED

(Exact name of registrant as specified in its charter)

Virginia	**54-1972729**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. employer identification no.)**
10 Finderne Avenue, Building 10 Bridgewater, New Jersey 08807	**(908) 977-9900**
(Address of principal executive offices)	**(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 $0.01 per share	**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 [ü] No [ ]

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes [ ] No [ü]

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 [ü] 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 [ü] No [ ]

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K 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 small reporting company (See the definitions of "large accelerated filer," "accelerated filer," and "small reporting company" in Rule 12b-2 of the Exchange Act). Large accelerated filer [ü] Accelerated filer [ ] Non-accelerated filer [ ] Small 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 [ü]

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant on June 30, 2014, was $772.7 million (based on the closing price for shares of the registrant's Common Stock as reported on the Nasdaq Global Select Market on that date). In determining this figure, the registrant has assumed solely for this purpose that all of its directors, executive officers, persons beneficially owning 10% or more of the outstanding Common Stock and certain other stockholders of the registrant may be considered to be affiliates. This assumption shall not be deemed conclusive as to affiliate status for this or any other purpose.

On February 2, 2015, there were 49,994,137 shares of the registrant's common stock, $0.01 par value, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for its 2015 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission no later than 120 days, or April 30, 2015, after the registrant's fiscal year ended December 31, 2014, and to be delivered to shareholders in connection with the 2015 Annual Meeting of Shareholders, are herein incorporated by reference in Part III of this Form 10-K.

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In this Form 10-K, we use the words "Insmed Incorporated" to refer to Insmed Incorporated, a Virginia corporation, and we use the words "Company," "Insmed," "Insmed Incorporated," "we," "us" and "our" to refer to Insmed Incorporated and its consolidated subsidiaries. Insmed, ARIKACE, ARIKAYCE, and IPLEX are trademarks of Insmed Incorporated. This Form 10-K also contains trademarks of third parties. Each trademark of another company appearing in this Form 10-K is the property of its owner.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward looking statements. "Forward-looking statements," as that term is defined in the Private Securities Litigation Reform Act of 1995, are statements that are not historical facts and involve a number of risks and uncertainties. Words herein such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "intends," "potential," "continues," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) identify forward-looking statements.

Forward-looking statements include, but are not limited to: our ability to complete development of, receive regulatory approval for, and successfully commercialize ARIKAYCE, or liposomal amikacin for inhalation (LAI), and INS1009, inhaled treprostinil prodrug; our estimates of expenses and future revenues and profitability; our plans to develop and market new products and the timing of these development programs; status, timing, and the results of preclinical studies and clinical trials and preclinical and clinical data described herein; the timing of responses to information and data requests from the US Food and Drug Administration (the "FDA"), the European Medicines Agency ("the EMA"), and other regulatory authorities; our clinical development of product candidates; our ability to obtain and maintain regulatory approval for our product candidates; our expectation as to the timing of regulatory review and approval; our estimates regarding our capital requirements and our needs for additional financing; our estimates of the size of the potential markets for our product candidates; our selection and licensing of product candidates; our ability to attract third parties with acceptable development, regulatory and commercialization expertise; the benefits to be derived from corporate license agreements and other third party efforts, including those relating to the development and commercialization of our product candidates; the degree of protection afforded to us by our intellectual property portfolio; the safety and efficacy of our product candidates; sources of revenues and anticipated revenues, including contributions from license agreements and other third party efforts for the development and commercialization of products; our ability to create an effective direct sales and marketing infrastructure for products we elect to market and sell directly; the rate and degree of market acceptance of our product candidates; the timing, scope and rate of reimbursement for our product candidates; the success of other competing therapies that may become available; and the availability of adequate supply and manufacturing capacity and quality for our product candidates.

Forward-looking statements are based upon our current expectations and beliefs, and involve known and unknown risk, uncertainties and other factors, which may cause our actual results, performance and achievements and the timing of certain events to differ materially from the results, performance, achievements or timing discussed, projected, anticipated or indicated in any forward-looking statements. Such factors include, among others, the factors discussed in Item 1A "Risk Factors" as well as those discussed in Item 7 under the section entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere throughout this Annual Report on Form 10-K. We caution readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the Securities and Exchange Commission, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

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PART I

ITEM 1. BUSINESS

Business Overview

Insmed is a biopharmaceutical company dedicated to improving the lives of patients battling serious lung diseases. We are focused on the development and commercialization of ARIKAYCE, or liposomal amikacin for inhalation (LAI), for at least two identified orphan patient populations: patients with nontuberculous mycobacteria (NTM) lung infections and cystic fibrosis (CF) patients with *Pseudomonas aeruginosa (Pseudomonas)* lung infections. We are also focused on the development of INS1009, an inhaled treprostinil prodrug. Treprostinil is a prostacyclin used in the treatment of pulmonary arterial hypertension (PAH), a chronic, life-threatening disorder characterized by abnormally high blood pressure in the arteries between the heart and lungs.

In March 2014, we reported top-line clinical results from the double-blind portion of our phase 2 clinical trial in the United States (US) and Canada of ARIKAYCE in patients who had treatment-resistant lung infections caused by NTM. The randomized, double-blind, placebo-controlled phase 2 clinical trial compared ARIKAYCE (590 mg delivered once daily), added to standard of care treatment, versus standard of care treatment plus placebo, in 90 adult patients with treatment resistant NTM lung disease. Eligibility for the study required patients to have been on the American Thoracic Society/Infectious Disease Society of America guideline therapy for at least six months prior to screening and to continue to have persistently positive mycobacterial cultures. The primary efficacy endpoint of the study was a semi-quantitative measurement of the change in mycobacterial density on a seven-point scale from baseline (day one) to the end of the randomized portion of the trial (day 84). ARIKAYCE did not meet the pre-specified level for statistical significance of the primary efficacy endpoint, although there was a positive trend (p=0.148) in favor of ARIKAYCE. A secondary efficacy endpoint of the study was proportion of subjects with culture conversion to negative. ARIKAYCE achieved statistical significance with regard to this secondary endpoint, with 11 out of 44 patients treated with ARIKAYCE (added to standard of care treatment) demonstrating clearance of the infecting mycobacterial organism (culture negative) at day 84 of the study as compared to 3 out of 45 patients treated with placebo (added to standard of care treatment) (p=0.01).

In May 2014, additional data from the open-label portion of the phase 2 trial were presented in a poster session at the American Thoracic Society meeting. At the conclusion of the 84-day double blind phase of the trial, 78 of the 80 patients completing the double-blind phase agreed to receive once-daily ARIKAYCE plus standard of care treatment for an additional 84 days. Data from 68 of these patients who completed the visits during the additional open label phase were available for inclusion in the poster. These results collected from the open label phase show that 21 of these patients were culture negative for NTM at Day 168. This data reflects 10 patients who were culture negative at Day 84 as well as 5 additional patients from the ARIKAYCE arm and 6 additional patients who were initially on placebo and switched to ARIKAYCE during the open-label phase.

In June 2014, the US Food and Drug Administration (FDA) granted ARIKAYCE Breakthrough Therapy Designation for the treatment of adult patients with NTM lung disease who are treatment refractory. This designation is based on findings from our U.S. phase 2 clinical trial of ARIKAYCE to treat NTM lung infections. ARIKAYCE has already received Orphan Drug, Qualified Infectious Disease Product (QIDP) and Fast Track designations from the FDA for the treatment of NTM lung infections and has also received Orphan Drug Designation from the European Medicines Agency (EMA).

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In the fourth quarter of 2014, we filed a Marketing Authorization Application (MAA) with the EMA for ARIKAYCE for the treatment of NTM lung infections as well as *Pseudomonas* lung infections in CF patients. The MAA for ARIKAYCE was validated in February 2015 after the EMA's pediatric committee approved the Pediatric Investigation Plan (PIP) for ARIKAYCE. The validation of the MAA filing is the start of the formal review process by the EMA.

In addition, following discussions with the FDA, we have commenced a phase 3 randomized, open-label, global study which is designed to confirm the positive culture conversion results seen in our phase 2 clinical trial. This confirmatory study is investigating ARIKAYCE for use in non-CF patients 18 years and older with *Mycobacterium avium* complex (MAC) NTM lung infections who have thus far failed to achieve culture conversion on a multi-drug treatment regimen. This subgroup of patients in the phase 2 trial responded particularly well to treatment with ARIKAYCE. We believe this approach will confirm the previous study results and could provide a path to filing and approval for an indication in patients with NTM who are refractory to treatment. Following discussions with the FDA, the primary efficacy endpoint will be proportion of patients achieving culture conversion, with additional goals of demonstrating sustainability and safety. The protocol for the phase 3 trial was agreed upon following dialogue with the FDA and was approved by the U.S. Central Institutional Review Board (IRB). We initiated the global trial in early 2015 and expect to complete enrollment within one year. We anticipate having preliminary top-line clinical results from the confirmatory phase 3 study in mid-2016. If the study meets the primary endpoint of culture conversion, we believe we would be eligible to submit a new drug application pursuant to 21 CFR 314 Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) which permits FDA to approve a drug based on a "surrogate endpoint" provided the sponsor commits to post-market studies to verify and describe the drug's clinical benefit. We expect to conduct the trial at over eighty sites including the United States, Europe, Australia, Japan and Canada with enrollment of approximately 300 patients.

In addition to ARIKAYCE, we believe that we can apply our proven design and development expertise to advance INS1009, an investigational sustained-release inhaled treprostinil prodrug that has the potential to address certain of the current limitations of existing inhaled prostanoid therapies in PAH. We believe that INS1009 may prolong duration of effect and may provide greater consistency in pulmonary arterial pressure reduction over time. Current inhaled prostanoid therapies must be dosed four to nine times per day. Reducing dose frequency therefore has the potential to ease patient burden and to positively impact compliance. Additionally, we believe that INS1009 over time may reduce side effects, including elevated heart rate, low blood pressure, and severity and/or frequency of cough, associated with high initial drug levels when using current inhaled prostanoid therapies.

In late 2014, we had a pre-investigational new drug (pre-IND) meeting with the FDA for INS1009 and clarified that, subject to final review of the pre-clinical data, INS1009 could be eligible for approval under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) ("505(b)(2) approval"). Like a traditional NDA that is submitted under Section 505(b)(1) of the FDCA, a 505(b)(2) NDA must include full safety and effectiveness reports, but unlike a traditional NDA the applicant may rely at least in part on studies not conducted by or for the applicant. The ability to rely on existing data to support safety and/or effectiveness can reduce the time and cost associated with traditional NDAs. We are conducting preclinical work and toxicology evaluations related to the unique formulation and route of administration and if results from these studies support continued product development, we may continue advancing the program with the goal of submitting an investigational new drug (IND) application and commencing a phase 1 trial in the second half of 2015.

We also plan to develop, acquire, in-license or co-promote other products that address orphan or rare diseases possibly in the fields of pulmonology and infectious disease. Our current primary development focus is to obtain regulatory approval for ARIKAYCE in the U.S. for the NTM indication

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and in Europe for the NTM and CF indications, enroll and complete our global phase 3 NTM study, and prepare for commercialization, assuming regulatory approval, in the US, Europe, Canada and Japan. We anticipate that, if approved, ARIKAYCE would be the first once-a-day inhaled antibiotic treatment option available for the CF indication and the NTM indication in the US, Europe or Canada.

The following table summarizes the current status of ARIKAYCE and INS1009 development:

Product Candidate/Target Indications	Status	Next Expected Milestones
ARIKAYCE Non-tuberculous mycobacteria (NTM) lung infections	We commenced a phase 3 global study (the "212 study") which is designed to confirm the positive culture conversion results seen in our phase 2 clinical trial. This confirmatory study is primarily investigating ARIKAYCE for use in the non-CF, treatment failure population with MAC NTM lung infections.	We expect to file an application in Canada during the second half of 2015 for the treatment of both NTM lung infections and *Pseudomonas* lung infections in CF patients.
		We expect to complete enrollment in the 212 study in approximately twelve months from the initiation of the trial.
	We have filed a MAA with the EMA, which was validated in February 2015.	
	We reported top-line clinical results from our phase 2 clinical trial which stated that ARIKAYCE did not meet the pre-specified level for statistical significance with respect to the primary endpoint, but did achieve statistical significance with regard to the clinically relevant key secondary endpoint of culture conversion.	If approved, we expect ARIKAYCE would be the first approved inhaled antibiotic treatment in the US, Canada and Europe for NTM lung infections.
		We are developing plans to commercialize ARIKAYCE, if approved, in certain countries in Europe, in the US, and Canada, and eventually Japan and certain other countries.
	Granted Breakthrough Therapy designation by the FDA.	
	Granted Orphan Drug designation by the FDA and EMA.	
	Granted Qualified Infectious Disease Product (QIDP) designation, which includes Priority Review, by the FDA.	
	Granted Fast Track designation by the FDA which permits a rolling submission of an NDA.	

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Product Candidate/Target Indications	Status	Next Expected Milestones
ARIKAYCE *Pseudomonas aeruginosa* lung infections in CF patients	We have filed a MAA with the EMA, which was validated in February 2015.	We expect to file an application in Canada during the second half of 2015 for the treatment of both NTM lung infections and *Pseudomonas* lung infections in CF patients.
	We reported top-line clinical results from our phase 3 clinical trial conducted in Europe and Canada, in which once-daily ARIKAYCE achieved its primary endpoint of non-inferiority when compared to twice-daily tobramycin inhaled solution.	We expect to announce final results from the two-year open label extension study in the second half of 2015.
	We are conducting a two-year, open-label safety study in patients who completed the phase 3 clinical trial. We expect to complete this study in mid-2015.	We are developing plans to commercialize ARIKAYCE, if approved, in certain countries in Europe and Canada where we expect it would be the only once-a-day treatment for *Pseudomonas* lung infections in CF patients.
	We reported top-line results from the patients who completed the first year of the two-year open label extension study.	We will initiate new studies in pediatric patients, however we currently do not plan to initiate any further studies in adult CF patients with *Pseudomonas* lung infections.
	Granted orphan drug designation by the EMA and FDA.	
INS1009 (inhaled treprostinil prodrug) *for pulmonary arterial hypertension (PAH)*	We completed a pre-investigational new drug (IND) meeting with the FDA for INS1009, and we have clarified that, subject to final review of the pre-clinical data, we would be eligible for a 505(b)(2) approval pathway.	We expect to file an IND in the second half of 2015.
		We expect to commence a phase 1 trial in the second half of 2015.

Corporate History

We were incorporated in the Commonwealth of Virginia on November 29, 1999. On December 1, 2010, we completed a business combination with Transave, Inc. (Transave) a privately held, New Jersey-based pharmaceutical company focused on the development of differentiated and innovative inhaled pharmaceuticals for the site-specific treatment of serious lung infections.

Our Strategy

Our strategy is to focus on the development and commercialization of innovative inhaled therapies for patients with serious lung diseases in orphan indications. While we believe that ARIKAYCE has the potential to treat many different diseases, our attention is initially focused on

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regulatory approval and commercialization preparation for our two initial indications: (1) NTM lung infections and (2) *Pseudomonas* lung infections in CF patients. Our current priorities are as follows:

- Continue conducting clinical trials to generate additional data supporting the safety and effectiveness of ARIKAYCE for the treatment of NTM lung infections and *Pseudomonas* lung infections in CF patients;
- Actively pursue approvals of ARIKAYCE to treat NTM lung infections through the submission of country-specific marketing authorizations to applicable regulatory bodies in the US, Europe, Canada, Japan and certain other countries;
- Actively pursue approval of ARIKAYCE to treat *Pseudomonas* lung infections in CF patients through the submission of marketing authorizations to applicable regulatory bodies in Europe and Canada;
- Expand our product supply chain in support of clinical development and if approved, commercialization;
- Prepare for commercial launch in the NTM indication in the US, Europe, Canada and eventually Japan and certain other countries;
- Prepare for commercial launch in *Pseudomonas* lung infections in CF patients indication in Europe and Canada;
- Attempt to develop, acquire, in-license or co-promote promising late stage or commercial products that we believe are complementary to ARIKAYCE and our core competencies; and
- Continue to develop novel formulations of existing therapies, where such reformulation could materially improve the treatment paradigm for the underlying disease, as we believe could be the case with INS1009 or enable pursuit of new indications.

In support of these priorities, we completed our registrational phase 3 clinical study of ARIKAYCE in CF patients with *Pseudomonas* lung infections in Europe and Canada. We submitted regulatory marketing applications for the CF and NTM indications in Europe and expect to file in Canada in the second half of 2015. In the first half of 2014, we completed our US and Canadian phase 2 clinical study of ARIKAYCE for the treatment of NTM lung infections in treatment refractory patients. Following recent discussions with the FDA, we initiated a global phase 3 clinical trial of ARIKAYCE in NTM which will be a confirmatory study for patients with NTM lung infections who have thus far failed their multi-drug treatment regimen. We plan to scale up manufacturing, we are identifying second source suppliers, and we plan to implement supply and quality agreements in preparation for commercialization of ARIKAYCE. In February 2014, we entered into a contract manufacturing agreement with Therapure Biopharma Inc. (Therapure) for the manufacture of ARIKAYCE at the larger scales necessary to support commercialization. In July 2014, we entered into a commercialization agreement with PARI Pharma GmbH (PARI), the manufacturer of our drug delivery nebulizer, to address our commercial supply needs. We have commenced the build-out of our commercial infrastructure in preparation for potential commercial launches in Europe, Canada and the US. We completed a pre-IND meeting with the FDA for INS1009, our investigational inhaled treprostinil prodrug for use in the treatment of PAH and we have clarified that, subject to final review of the pre-clinical data, we would be eligible for a 505(b)(2) approval pathway. And finally, we will continue to evaluate opportunities for additional products through various business development channels.

Product Candidates

Our lead product candidate, ARIKAYCE, or LAI, is a once-a-day inhaled antibiotic treatment engineered to deliver an anti-infective directly to the site of serious lung infections. There are two key components of ARIKAYCE: the liposomal formulation of the drug and the nebulizer device through which ARIKAYCE is inhaled via the mouth and into the lung. The nebulizer technology is owned by

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PARI, but through a licensing agreement we have exclusive access to this technology, which has been specifically developed for the delivery of ARIKAYCE. Our proprietary liposomal technology and the nebulizer are designed specifically for delivery of pharmaceuticals to the lung and provide for potential improvements to existing treatments. We believe that ARIKAYCE has potential usage for at least two orphan patient populations with high unmet need: patients who have NTM lung infections and CF patients who have *Pseudomonas* lung infections. We estimate the combined global market potential for these two orphan indications, subject to final approved labels, to be over $1 billion.

ARIKAYCE has the potential to be differentiated from amikacin and certain marketed drugs for the treatment of chronic lung infections if it can be demonstrated to provide improved efficacy, safety and patient convenience. We believe ARIKAYCE's ability to deliver high, sustained levels of amikacin directly to the lung and to the specific site of the underlying infection could distinguish it from other alternatives. We are also investigating ARIKAYCE's potential for durability of effect, benefiting patients when off treatment or for an extended period of treatment. In addition, the inhalation delivery of ARIKAYCE may reduce the potential for adverse events such as ototoxicity (hearing loss, ringing in the ears and/or loss of balance) and nephrotoxicity (toxicity to the kidneys), as compared with intravenous (IV) administration of amikacin. If approved, we expect that ARIKAYCE will be administered once-daily via inhalation using the eFlow® Nebulizer System. We believe that ARIKAYCE and the nebulizer system will reduce dosing frequency, as compared with the currently marketed inhaled antibiotics for CF indications, which require dosing two to three times daily with treatment times ranging from approximately 10 to 40 minutes per day. With once-daily administration we believe that ARIKAYCE can potentially improve patient compliance, which we believe may in turn lead to a reduction in the development of antibiotic resistance and, ultimately, lead to clinical and health economic benefits.

We believe that ARIKAYCE may provide: (i) improved efficacy resulting from sustained deposition of drug in the lung and improved ability to reach the site of infection (for CF *Pseudomonas* lung infections, this means penetration of biofilm and facilitated drug release by factors that are secreted by the bacteria, and for NTM, this means enhanced uptake into macrophages, targeting NTM within these cells); (ii) decreased adverse events and improved tolerability as compared with amikacin delivered intravenously, and (iii) reduced dosing frequency or treatment time as compared to existing inhaled products used by CF patients. In the future we may conduct head-to-head comparative studies that would be necessary to make comparative statements against other products.

Our second product candidate, INS1009, is an inhaled treprostinil prodrug that will address certain of the current limitations of inhaled prostanoid therapies in PAH. We believe that our inhaled treprostinil prodrug may prolong duration of effect and may provide greater consistency in pulmonary arterial pressure reduction over time. Current inhaled prostanoid therapies must be dosed four to nine times per day. Reducing dose frequency would therefore ease patient burden and may positively impact compliance. With a formulation where an active prostanoid is released over time, we believe the potential for side effects due to initially high drug levels is reduced. For example, there may be reduced change in heart rate, change in blood pressure, and the severity and/or frequency of cough, as compared to treatment with current inhaled prostanoid therapies. Pulmonary hypertension was the 10th most expensive specialty therapy class in the United States in 2013 and approximately 25% of patients are non-adherent to medication therapy. We estimate the global market for pulmonary hypertension therapies to be approximately $4.5 billion, with the market for inhaled products representing approximately $500 million.

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ARIKAYCE for Patients with NTM Lung Infections

Overview of NTM Lung Infections

Nontuberculous mycobacteria, or NTM, are organisms common in soil and water that have been associated with lung disease in select patient groups. NTM have characteristics that are similar to tuberculosis, or TB, but NTM are not believed to be contagious. Many people have NTM in their bodies, but NTM do not normally lead to an infection, perhaps because the body's immune system successfully overcomes the threat of infection. It is not completely understood why certain individuals are susceptible to NTM infections. However, the patients who become infected by NTM often are immune-compromised, due to comorbidities such as HIV or immune-modulating treatments for rheumatoid arthritis, or have structural damage in their lungs, due to smoking, chronic obstructive pulmonary disease or CF, at the time of the infection.

NTM are organisms that invade and multiply chiefly within macrophages. NTM lung infections are often chronic, debilitating and progressive requiring lengthy treatment periods and hospitalizations. Signs and symptoms of NTM pulmonary disease are variable and nonspecific. They include chronic cough, sputum production and fatigue. Less commonly, malaise, dyspnea, fever, hemoptysis, and weight loss can also occur, usually with advanced NTM disease. Evaluation is often complicated by the symptoms caused by co-existing lung diseases. According to a study published in the *American Journal of Respiratory and Critical Care Medicine*, these conditions include chronic obstructive airway disease associated with smoking, bronchiectasis, previous mycobacterial diseases, CF and pneumoconiosis (Olivier et al. 2003).

Current Treatment Options and Limitations

Amikacin sulfate is an FDA-approved antibiotic with proven efficacy in the treatment of a broad range of gram-negative infections, including *Pseudomonas* and NTM. ARIKAYCE is in the aminoglycoside class of antibiotics. We believe there currently is no drug approved in the US, Europe or Canada for treatment of NTM lung infections, and as a result all current drug treatments for NTM are used off-label. Patients are often treated with the same antibiotics that are used to treat TB. Such treatments usually consist of lengthy multi-drug antibiotic regimens, which are often poorly tolerated and not very effective, especially in patients with severe disease and patients who have failed prior treatments. NTM patients average 7.6 antibiotic courses per year (SDI Healthcare Database, July 2009). Treatment guidelines published in 2007 in the *American Journal of Respiratory and Critical Care Medicine* reported that few clinical trials were under way to identify treatment recommendations, and no new antibiotics had been studied for the treatment of NTM lung infections in multi-center, randomized clinical trials since the late 1990s.

Although approved for other indications, amikacin sulfate is not approved by the FDA for NTM lung infections. In practice, however, it is often recommended by physicians as part of the multi-drug treatment regimen for some NTM patients. Amikacin is delivered most commonly by intravenous administration and, less often, by inhalation. Because the drug is delivered for months at a time, resulting in sustained high systemic (blood) levels of amikacin, there can be considerable toxicity, including ototoxicity and nephrotoxicity, associated with intravenous treatment. There are few prior studies to support what doses should be administered to effectively treat NTM patients even with these existing medications and they are often titrated on a patient by patient basis. If approved for NTM patients, we expect ARIKAYCE would be the first and only approved inhaled antibiotic for the treatment of NTM lung infections in the US, Europe or Canada.

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Market

The prevalence of human disease attributable to NTM has increased over the past two decades. In 2012, in collaboration with the NIH, we funded a study performed by Clarity Pharma Research that showed there were an estimated 50,000 cases of pulmonary disease attributable to NTM in the US in 2011 and that such cases were estimated to be growing at a rate of 10% per year. NTM is four to five times more prevalent than TB in the US (Incidence of TB from Center for Disease Control and Prevention Morbidity and Mortality Weekly Report, March 2012). In a decade-long study, researchers found that the diagnosis of NTM in the US is increasing at approximately 8% per year and that those NTM patients over the age of 65 are 40% more likely to die than those who do not have the disease (Adjemian et al, Prevalence of Pulmonary Nontuberculous Mycobacterial Disease among Medicare Beneficiaries, USA, 1997-2007, American Journal of Respiratory and Critical Care Medicine, April 2012).

In 2013, we engaged Clarity Pharma Research to perform a similar chart audit study of NTM in Europe and Japan. Based on results of this study, researchers estimated that there are approximately 20,000 cases of pulmonary disease attributable to NTM within the European nations of France, Germany, the United Kingdom, Italy and Spain combined and approximately 30,000 in the 28 countries comprising the EU. In addition, there are nearly 32,000 cases in Japan. Although population-based data on the epidemiology of NTM infections in Europe are limited, consistent with US prevalence trends, recent published studies concur that prevalence in Europe is increasing and, according to a study published in the Japanese journal Kekkaku in 2011, Japan has one of the world's highest NTM disease rates.

Although there are many species of NTM that have been reported to cause lung infections, ARIKAYCE is intended to treat two of the most common, *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* (*M abscessus*). MAC accounts for the vast majority of NTM lung infections with prevalence rates from 72% to more than 85% in the US. The reported prevalence rates for *M. abscessus* range from 3% to 11% in the US. The diagnosed prevalence of NTM species causing lung infections varies geographically with MAC rates of 25% to 55% reported in Europe. MAC is also the most common NTM pathogen in Japan.

We are studying the economic and societal implications of NTM lung infections. We recently conducted a burden of illness study in the United States with a major medical benefits provider. This study has confirmed that NTM lung infections are costly to treat and manage. Active treatment of patients with NTM lung infection does result in significant medical expense savings as opposed to patients that are not treated. We plan to repeat this type of research globally in support of our overall disease awareness and education efforts.

ARIKAYCE for NTM Lung Infections: Potential Advantages and Distinguishing Features

If approved, we believe ARIKAYCE would be the first and only approved treatment in the US, Canada and Europe for patients battling NTM lung infections.

Liposomal Design and Formulation

We believe that ARIKAYCE may be effective in treating patients with NTM lung infections due to the apparent ability of the ARIKAYCE liposomes to be taken up inside lung macrophages that harbor NTM. Macrophages are immune cells whose primary function includes removing foreign particles and bacteria from the lungs. NTM are taken up by and multiply inside these macrophages. Many antibiotics cannot efficiently gain access to the macrophage interior. ARIKAYCE liposomes,

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however, are designed to be internalized by lung macrophages and thereby deliver high levels of drug inside the macrophages where the NTM bacteria are located.

Route of Administration

We believe ARIKAYCE has the potential to offer a safety profile different from that of intravenous delivery of amikacin. For example, unlike the intravenous administration of amikacin, ARIKAYCE would deliver the drug more directly to the site of disease. We anticipate this will result in less exposure of non-disease sites to amikacin. We believe this may reduce the potential for the occurrence of any drug-related systemic toxicity, such as nephrotoxicity, which is especially important with diseases like NTM that require long-term drug administration.

Anticipated Dosage Regimen

We believe ARIKAYCE, if approved, could improve patient convenience by providing once-a-day dosing. According to *SDI Healthcare Database* NTM patients average 7.6 antibiotic courses and 10.2 hospital days per year. We anticipate that ARIKAYCE will be administered once daily outside of the hospital until the NTM infection is eradicated and then for an additional period of one year, similar to the current multi-drug treatment guidelines. We believe that an effective inhaled treatment that improves the outcomes for an NTM patient would represent a significant benefit in the patient's quality of life.

Current Clinical Program

In the fourth quarter of 2014, we filed a MAA with the EMA for ARIKAYCE for the treatment of NTM lung infections as well as *Pseudomonas* lung infections in CF patients. The MAA for ARIKAYCE was validated in February 2015 after the EMA's pediatric committee approved the PIP for ARIKAYCE. The validation of the MAA filing is the start of the formal review process by the EMA.

In early 2015, following discussions with the FDA, we have commenced a phase 3 randomized, open-label, global study which is designed to confirm the positive culture conversion results seen in our phase 2 clinical trial. This confirmatory study is investigating ARIKAYCE for use in non-CF patients 18 years and older with MAC NTM lung infections who have thus far failed to achieve culture conversion on a multi-drug treatment regimen. This subgroup of patients in the phase 2 trial responded particularly well to treatment. We believe this approach will confirm the previous study results and provide a path to filing and approval for an indication in patients with NTM who are refractory to treatment. Following discussions with the FDA, the primary efficacy endpoint will be proportion of patients achieving culture conversion, with additional goals of demonstrating sustainability and safety. The protocol for the phase 3 trial was agreed upon following dialogue with the FDA and was approved by the U.S. Central IRB. We initiated the global trial in early 2015 and expect to complete enrollment within one year. We anticipate having preliminary top-line clinical results from the confirmatory phase 3 study in mid-2016. If the study meets the primary endpoint of culture conversion, we believe we would be eligible to submit a new drug approval application pursuant to 21 CFR 314 Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) which permits FDA to approve a drug based on a "surrogate endpoint" provided the sponsor commits to post-market studies to verify and describe the drug's clinical benefit. We expect to conduct the trial at over eighty sites including the United States, Europe, Australia, Japan and Canada.

The 212 study is expected to enroll and randomize approximately 300 patients, with approximately 200 patients receiving ARIKAYCE once daily in addition to their current multi-drug treatment regimen and approximately 100 patients receiving only their current multi-drug treatment

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regimen. The primary efficacy endpoint in this open-label study will be proportion of patients achieving culture conversion by six months, which will allow for a NDA submission following data analysis. The definition of culture conversion is three consecutive monthly negative cultures. Patients in each arm who convert will continue their treatment for a total of twelve months from their first negative culture. Patients in each arm who do not convert have the option to continue in a follow-on study (the "312" follow-on study) for an additional twelve months of treatment with ARIKAYCE, in addition to the multi-drug regimen. The 312 follow-on study will be used to evaluate longer term safety of ARIKAYCE treatment.

In March 2014, we reported top-line clinical results from the double-blind portion of our phase 2 clinical trial in the US and Canada of ARIKAYCE in patients who have lung infections caused by NTM. The randomized, double-blind, placebo-controlled phase 2 clinical trial compared ARIKAYCE (590 mg delivered once daily), added to standard of care treatment, versus standard of care treatment plus placebo, in 90 adult patients with treatment resistant NTM lung disease. Eligibility for the study required patients to have been on the American Thoracic Society/Infectious Disease Society of America guideline therapy for at least six months prior to screening and to continue to have persistently positive mycobacterial cultures. The primary efficacy endpoint of the study was a semi-quantitative measurement of the change in mycobacterial density on a seven-point scale from baseline (day one) to the end of the randomized portion of the trial (day 84). ARIKAYCE did not meet the pre-specified level for statistical significance of the primary endpoint, although there was a positive trend in favor of ARIKAYCE. A secondary efficacy endpoint of the study was proportion of subjects with culture conversion to negative. ARIKAYCE achieved statistical significance with regard to this secondary endpoint, with 11 out of 44 patients treated with ARIKAYCE (added to standard of care treatment) demonstrating negative cultures at day 84 of the study as compared to 3 out of 45 patients treated with placebo (added to standard of care treatment).

In May 2014, additional data from the open-label portion of the phase 2 trial were presented in a poster session at the American Thoracic Society meeting. At the conclusion of the 84-day double blind phase of the trial, 78 of the 80 patients completing the double-blind phase agreed to receive once-daily ARIKAYCE plus standard of care treatment for an additional 84 days. Data from 68 of these patients who completed the visits during the additional open label phase were available for inclusion in the poster. These results collected from the open label phase show that 21 of these patients were culture negative for NTM at Day 168. This data reflects 10 patients who were culture negative at Day 84 as well as 5 additional patients from the ARIKAYCE arm and 6 additional patients who were initially on placebo and switched to ARIKAYCE during the open-label phase.

In June 2014, the FDA granted ARIKAYCE, Breakthrough Therapy Designation for the treatment of adult patients with NTM lung disease who are treatment refractory. This designation is based on findings from our U.S. phase 2 clinical trial of ARIKAYCE to treat NTM lung infections. ARIKAYCE has already received Orphan Drug, Qualified Infectious Disease Product (QIDP) and Fast Track designations from the FDA for the treatment of NTM lung infections and recently received Orphan Drug Designation from the EMA.

Additionally, we are conducting a separate scintigraphy sub-study to examine drug deposition and distribution of ARIKAYCE in the lung with the PARI nebulizer.

Development History

Nonclinical evaluations of ARIKAYCE in relation to NTM infections indicate: (1) high concentrations of drug are deposited in the lung, and high levels are sustained for prolonged periods,

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with low serum concentrations, and (2) ARIKAYCE has *in vitro* activity that is superior to amikacin solution against different strains of NTM.

Data obtained from *in vitro* testing of ARIKAYCE with respect to four different strains of MAC and *M. abscessus* indicate dose response with ARIKAYCE and superior activity to amikacin in solution. We believe that the safety and efficacy data obtained from the phase 2 study in NTM patients, the phase 3, phase 2 and open label studies of ARIKAYCE in CF, the phase 2 study in non-CF patients with chronic lung disease and pulmonary infections, and the non-clinical data collected to date serve as the basis for further development of ARIKAYCE in patients with NTM lung infections.

In 2011, we submitted an IND to launch a phase 3 study of ARIKAYCE in CF and non-CF patients for the treatment of NTM lung infections in treatment refractory patients. In August 2011, prior to starting the NTM study, we announced that the FDA placed a clinical hold on our phase 3 trial. The clinical hold for the NTM study was lifted in January 2012. The FDA based its clinical hold decision on an initial review of the results of a long-term rat inhalation carcinogenicity study with ARIKAYCE. When rats were given ARIKAYCE daily by inhalation for two years, 2 of the 120 rats receiving the highest dose developed lung tumors. These rats received ARIKAYCE doses that were within two-fold of those in clinical studies (normalized on a body surface area basis or a lung weight basis). ARIKAYCE was not associated with changes that may lead to tumors in shorter-term studies in animals. Additionally, ARIKAYCE was not shown to be genotoxic in our standard series of tests. The relevance of the observed rat tumors to the use of ARIKAYCE in humans is not known. The FDA requested we conduct a phase 2 clinical trial, instead of our previously agreed upon phase 3 clinical trial in adult NTM patients, to provide proof-of-concept efficacy and safety data for ARIKAYCE in NTM patients. Despite the change in status from phase 3 to phase 2, the study design and target enrollment did not change. In connection with the FDA's decision to lift the clinical hold for all disease indications, we agreed to conduct a dog inhalation toxicity study of ARIKAYCE. In 2013, we concluded the dog inhalation toxicity study. In summary, the final report from the study stated that the lung macrophage response in dogs was similar to that seen in our previous 3 month dosing dog study, and there was no evidence of neoplasia, squamous metaplasia or proliferative changes.

Strategy for Commercialization

We currently plan to retain marketing rights for ARIKAYCE for the NTM indication. Given the current lack of approved treatments for NTM lung infections, we believe we will have a rapid and strong market position if ARIKAYCE is approved for commercialization in the NTM indication. We believe ARIKAYCE will require a limited commercial infrastructure because of the small focused nature of the potential physician prescribing population for NTM patients. We have commenced preparations for the potential commercialization of ARIKAYCE and we have filled several positions to support our future sales and marketing efforts. We may also seek to out-license ARIKAYCE in certain countries in Europe, as well as outside of Europe, Canada and the US. We estimate the potential global market for NTM therapies could be approximately $1 billion.

ARIKAYCE for CF Patients with *Pseudomonas* Lung Infections

Overview of CF and Pseudomonas Lung Infections

CF is an inherited chronic disease that is often diagnosed before the age of two. CF occurs primarily in individuals of central and western European origin. CF affects roughly 70,000 children and adults worldwide, including 30,000 children and adults in the US (Cystic Fibrosis Foundation Patient Registry, 2011) and 35,000 patients in Europe (Hoiby, BMC Medicine, 2011, 9:32). There is no cure for CF.

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Despite extensive treatment with multiple antibiotics, improved nutrition, and other treatments, life expectancy of a CF patient is only 38-40 years (Cystic Fibrosis Foundation Patient Registry, 2012). Median predicted age of survival is calculated using life table analysis (as calculated by actuaries) given the ages of the patients in the registry and the distribution of deaths. Using this calculation, half of the people in the patient registry are expected to live beyond the median predicted survival age, and half are expected to live less than the median predicted survival age.

Among other issues, CF causes thick, sticky mucus to develop in and clog the lungs. This creates an ideal environment for various pathogens, such as *Pseudomonas*, to colonize and lead to chronic infection of the lung, inflammation and progressive loss of lung function. In fact, chronic bronchial infections with *Pseudomonas* are a major cause of morbidity and mortality among patients with CF. Once a CF patient acquires a *Pseudomonas* infection, it is difficult to eradicate. The current, best available treatment is chronic administration of antibiotics to suppress the bacteria, reduce inflammation and preserve lung function for as long as possible. The rate of infection with *Pseudomonas* in CF patients increases with age. It is estimated that 80% of adult CF patients have chronic infection due to *Pseudomonas* (CFF Patient Registry, 2012). A study reported in the *Journal of Cystic Fibrosis* (Liou, 2010) found that deterioration in lung function of CF patients is the main cause of death and that, despite best efforts, lung function declines by 1% to 3% annually.

Current Treatment Options and Limitations

CF therapy significantly impacts patients' quality of life. Patients generally receive extensive antibiotic treatments, which can be delivered via the oral, intravenous and inhaled routes. Some CF patients spend up to three hours per day taking medications and other treatments, including inhaled antibiotics, and often face the burden of taking in excess of 20 pills per day. All currently approved inhalation treatments for *Pseudomonas* lung infections require two- to three-times a day dosing. If approved for CF patients with *Pseudomonas* lung infections, we expect ARIKAYCE would be the first inhaled antibiotic to be approved for once-daily administration in this indication.

Antibiotics delivered via inhalation are part of the standard treatment for CF patients with *Pseudomonas* lung infections and are generally thought to be a way to deliver more active drug directly to the site of infection compared with other routes of administration. The most used treatment in the US for the management of chronic *Pseudomonas* infection in subjects with CF is suppressive therapy with tobramycin. One example is twice daily Tobi inhaled solution, which is approved by the FDA for CF patients ages six years and above with a forced expiratory volume in 1 second ("FEV_1") of 25%-75%, has been sold in the US since January 1998. A 1999 study reported that Tobi, 300 mg, administered twice a day for cycles of 28 days followed by 28-days-off treatment was shown to reduce *Pseudomonas* colony counts, increase FEV_1 percent predicted, reduce hospitalizations and decrease additional antibiotic use (Ramsey et al., 1999, New England Journal of Medicine). High levels of tobramycin can be attained in the lung with relatively low systemic exposure with inhaled drug compared to intravenous tobramycin. However, patients using Tobi must be dosed twice a day for approximately 15 to 20 minutes of inhalation session per dose for a total of approximately 30 to 40 minutes per day. Recent data show that the effect of Tobi on pulmonary function in CF patients has lessened since its introduction into the marketplace more than a decade ago (Konstan et al., Journal of Cystic Fibrosis, January 2011, and Assael et al., 34th European Cystic Fibrosis Society Conference, Poster 86, June 2011). In addition, according to information presented at a FDA advisory panel, resistance to Tobi has increased 85% in the ten-year period from 1999 to 2009 (FDA advisory panel US-FDA-AIDAC for Tobi-Podhaler, September 2012).

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Market

We estimate that the global market for the treatment of *Pseudomonas* lung infections in CF patients is approximately $400 million. We believe this market is being driven by physicians' desire to maintain the lung function of CF patients, which continues to decline in many patients despite extensive treatment with current therapies including currently approved inhaled antibiotics. We believe that the following additional factors may lead to further market growth:

- Better patient adherence to physician prescribed regimens resulting from more convenient (less frequent and less time consuming) treatments;
- Physicians initiating treatment with inhaled antibiotics earlier for patients with *Pseudomonas* in their lungs;
- CF patients living longer;
- Physicians moving to a different antibiotic every other month as opposed to giving patients off-treatment holidays on alternate months; and
- The standard of care in the rest of the world continuing to advance closer to that in the EU and the US.

ARIKAYCE for CF Patients with Pseudomonas Lung Infections: Potential Advantages and Distinguishing Features

Patient Compliance Considerations

We believe ARIKAYCE may facilitate better patient compliance with prescribed treatment regimens; patient compliance with or "adherence" to prescribed treatment is generally expected to impact the effectiveness of treatment. If a product can improve adherence, it may be able to differentiate itself from other marketed drugs. In the case of treatment and management of chronic *Pseudomonas* lung infections in CF patients, currently the most used treatment in the US is suppressive therapy with 300 mg twice daily of Tobi inhaled solution and 112 mg twice daily tobramycin inhaled powder. Tobi is administered twice daily for 28 days followed by a 28-day-off period. This cycle of "on and off" treatment is repeated in a chronic pattern. We anticipate that ARIKAYCE would be administered once daily for 28 days followed by a 28-day off-drug period. We believe that any inhaled treatment that reduces the treatment burden on a CF patient could represent a significant improvement in the patient's quality of life and result in improved compliance, as well as reduce the development of antibiotic resistance.

Liposomal Design and Formulation

We believe ARIKAYCE has the potential to deliver high levels of amikacin directly to the site of bacteria in the lung for a sustained period of time, which we expect would differentiate it from other marketed drugs for the treatment of chronic *Pseudomonas* lung infections in CF patients. Current inhaled antibiotics are commonly used as standard treatments for CF patients with *Pseudomonas* lung infections and generally are thought to be a way to deliver more drug directly to the site of infection as compared with other methods of delivery. However, CF patients seldom clear the *Pseudomonas* permanently from their lungs, in part because of the thick sticky mucus these patients produce in their lungs, and often become chronically infected despite existing antibiotic treatments. All existing aminoglycoside antibiotics, including tobramycin and amikacin, are positively charged and tend to bind to the negative surfaces of mucus and the biofilm. In contrast, we have designed ARIKAYCE to be a neutrally charged liposome, which has been shown in laboratory studies, to penetrate both CF mucus and a *Pseudomonas* biofilm. This means that ARIKAYCE may reach the site of the *Pseudomonas*

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infection in CF patients' lungs more efficiently than the other currently available aminoglycoside antibiotics, including currently available inhaled antibiotics.

In addition, ARIKAYCE has demonstrated a prolonged half-life in animals' lungs. We believe this effect is due to our proprietary liposomal technology. One important measure of the effectiveness of antibiotics is the maintenance of anti-bacterial drug levels in the lung above the minimum inhibitory concentration. We anticipate that ARIKAYCE will be maintained in the human lung in a manner similar to what was demonstrated in animal studies.

We believe ARIKAYCE may be further differentiated from other marketed drugs for the treatment of chronic *Pseudomonas* lung infections in CF patients due to improved lung function during both on-treatment and off-treatment cycles. Typically an inhaled antibiotic is given to CF patients with chronic *Pseudomonas* lung infections for 28 days followed by a 28-day off-treatment cycle, which is often repeated chronically or for the rest of a patient's life. In February 2014, we reported interim data from our two-year open label extension study which showed a mean increase in relative change in FEV_1 which was sustained during both on-treatment and off-treatment months. In addition, during phase 2 studies ARIKAYCE demonstrated statistically significant and clinically meaningful improvement in pulmonary function throughout the 28-day treatment period, and such improvement was sustained during the 28-days off treatment period.

We have also reported data showing durability of effect for longer off-treatment periods. In an open-label phase 2 extension trial (TR02-105), CF patients using ARIKAYCE demonstrated sustained efficacy in lung function improvement during a 28-day treatment period and 56-day off-treatment period across multiple cycles of therapy as compared to baseline. In this clinical study, ARIKAYCE produced an improvement in lung function that was sustained over six cycles totaling approximately 17 months. During the off-treatment periods for this study, approximately 50% to 70% of the benefit achieved during the on-treatment periods was sustained at the end of the off-treatment periods. To our knowledge, no other inhaled antibiotic has shown sustained improvement in lung function at the end of a 56-day off-treatment period.

Route of Administration

We believe ARIKAYCE has the potential to offer a safety profile different from that of intravenous delivery of aminoglycosides. *Pseudomonas* is susceptible to several broad spectrum antibiotics, notably aminoglycosides. Some examples of aminoglycoside antibiotics include tobramycin and amikacin. Studies found that aminoglycosides are an important class of antibiotics for the treatment of *Pseudomonas* lung infections in CF patients because of their broad antimicrobial activity and concentration dependent bactericidal activity (Lacy et al., 1998; Lortholary et al., 1995; Zembower et al., 1998). Intravenous antibiotics were originally used for treatment of chronic infections associated with CF and are still used for pulmonary exacerbations. Studies report that ototoxicity and nephrotoxicity are common adverse events associated with the use of intravenous aminoglycosides and these effects are related to plasma drug levels (Mingeot-Leclercq and Tulkens, 1999).

There are two main obstacles to effective and safe treatment of CF:

- Drug Resistance. High-level multi-drug resistance complicates eradication of such strains from the bronchial secretions of CF patients. *Pseudomonas* lung infections are commonly treated using aminoglycoside antimicrobial agents, such as amikacin and tobramycin. However, due to drug resistance, significantly higher concentrations of these drugs above the minimum inhibitory concentration are required at the site of infection. The intravenous dosage levels required to achieve such exposures can be nephrotoxic and ototoxic.

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- Limited Penetration. There is limited penetration into and through the sputum/biofilm matrix by aminoglycoside antibiotics. The antibiotics are positively charged and the biofilm is negatively charged. As a result, the antibiotics bind to the biofilm and the availability of the drug at the location of the microorganism is suboptimal. We believe that our proprietary liposomal technology will result in localized targeting of drugs, leading to increased availability of the drug at the location of the microorganism, while significantly reducing drug exposure at non-disease sites throughout the body and reducing the occurrence of systemic drug-related toxicity.

Current Clinical Program

In the fourth quarter of 2014, we filed a MAA with the EMA for ARIKAYCE for the treatment of NTM lung infections as well as *Pseudomonas* lung infections in CF patients. The MAA for ARIKAYCE was validated in February 2015 after the EMA's pediatric committee approved the PIP for ARIKAYCE. The validation of the MAA filing is the start of the formal review process by the EMA.

We completed a registrational phase 3 clinical trial of ARIKAYCE for CF patients with *Pseudomonas* lung infections in Europe and Canada during the second quarter of 2013. The phase 3 trial was a randomized, open label, multi-center study designed to assess the comparative safety and efficacy of once-daily ARIKAYCE administered for approximately 13 minutes via the eFlow Nebulizer System and twice-daily Tobi (tobramycin inhalation solution) administered for approximately 15 minutes per treatment via the PARI LC Plus Nebulizer System for a daily total of approximately 30 minutes per day in CF patients with *Pseudomonas*. A total of 302 adult and pediatric CF patients with chronic *Pseudomonas* were randomized to receive 28-days of ARIKAYCE treatment or Tobi delivered twice-daily via the PARI LC Plus® Nebulizer System over a 24-week treatment period. The primary endpoint of the study was relative change in FEV_1 measured after three treatment cycles, with each cycle consisting of 28 days "on" treatment and 28 days "off" treatment. The study was designed to demonstrate non-inferiority to Tobi at a 5% non-inferiority margin with 80% power agreed upon by us and the EMA. Secondary endpoints measured were relative changes in FEV_1 at other time points, time to and number of pulmonary exacerbations, time to antibiotic rescue treatment, change in density of *Pseudomonas* in sputum, respiratory hospitalizations and changes in Patient Reported Outcomes assessing Quality of Life. Top-line results from this study indicated:

- ARIKAYCE achieved its primary endpoint of non-inferiority to Tobi for relative change in FEV_1 from baseline to the end of the study;
- Overall, secondary endpoints, as summarized above, showed comparability of once-daily ARIKAYCE compared with twice-daily Tobi; and
- The safety profile of ARIKAYCE was comparable to Tobi during all three treatment cycles, with adverse events consistent with those seen in similar studies and expected in a population of CF patients receiving inhaled antibiotics. There was no difference between arms in the reporting of serious adverse events and there were no unexpected adverse events.

We are conducting a two-year, open label safety study in patients that also completed our registrational phase 3 clinical study of ARIKAYCE for CF patients with *Pseudomonas* lung infections in Europe and Canada. Approximately 75% of the eligible patients that completed our registrational phase 3 clinical study consented to participate in the safety study. The patients in this study will receive ARIKAYCE for up to an additional two year period, using the same cycles of a 28 day on-treatment period and a 28 day off-treatment period. In February 2014, we reported interim data from our two-year open label extension study which showed a mean increase in relative change in FEV_1 which was sustained during both on-treatment and off-treatment months. This interim data was included as part of our regulatory filings with the EMA, which we filed in December 2014 and we plan to use this

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data in our filings with Health Canada, which we expect to submit in the second half of 2015. We expect to complete this study in mid-2015.

ARIKAYCE has been granted orphan drug status in the US and Europe for the treatment of *Pseudomonas* lung infections in CF patients.

Development History

Nonclinical evaluations of ARIKAYCE in relation to *Pseudomonas* lung infections indicate:

- High concentrations of drug are deposited in the lung, and high levels are maintained for prolonged periods, with low serum concentrations;
- ARIKAYCE penetrates CF sputum and *Pseudomonas* biofilm;
- ARIKAYCE exhibits antipseudomonal activity in *in vitro* and *in vivo* models, including against resistant isolates; and
- Virulence factors secreted by *Pseudomonas* facilitate the release of amikacin from ARIKAYCE.

Our predecessor liposomal amikacin formulations for inhalation were evaluated in a series of phase 1 clinical studies involving healthy volunteers and CF patients with *Pseudomonas* lung infections. The current formulation of ARIKAYCE was evaluated in phase 2 clinical studies in CF patients with *Pseudomonas* lung infections. We completed two randomized, placebo-controlled phase 2 studies with ARIKAYCE in 105 CF patients with chronic *Pseudomonas* lung infections in Europe and the US. In these studies, patients in the ARIKAYCE 560 mg cohort demonstrated statistically significant and clinically meaningful improvement in lung function throughout the 28-day on-treatment period compared with placebo. In addition, the improvement in lung function that was achieved at the end of the 28-day on-treatment period was sustained during the 28-day off-treatment period and was statistically significantly better than placebo.

In a separate follow-on open-label, multi-cycle clinical trial conducted in Europe, ARIKAYCE was given at a dose of 560 mg once daily via an eFlow Nebulizer System for six cycles which consisted of a 28-day on-treatment and 56-day off-treatment period, which is double the standard 28-day off-treatment period. In this clinical study, ARIKAYCE produced a statistically significant improvement in lung function that was sustained over the six cycles (approximately 17 months). In addition, approximately 50% to 70% of the benefit achieved during the 28-day on-treatment periods was sustained at the end of the 56-day off-treatment periods. In other words, ARIKAYCE demonstrated sustained efficacy in lung function improvement during the treatment and off-treatment periods across multiple cycles of therapy. To our knowledge, no other inhaled antibiotic has shown sustained improvement in lung function at the end of a 56-day off-treatment period. In addition, ARIKAYCE was well tolerated with overall adverse events reported as consistent with those expected in a population of CF patients receiving other inhaled medicines.

In August 2011, we announced that the FDA placed a clinical hold on our phase 3 trial for ARIKAYCE in CF patients with *Pseudomonas* lung infections, which was lifted in May 2012. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical trial or suspend an ongoing clinical trial. The FDA based its clinical hold decision on an initial review of the results of a long-term rat inhalation carcinogenicity study with ARIKAYCE. When rats were given ARIKAYCE daily by inhalation for two years, 2 of the 120 rats receiving the highest dose developed lung tumors. These rats received ARIKAYCE doses that were within two-fold of those in clinical studies (normalized on a body surface area basis or a lung weight basis). ARIKAYCE was not associated with changes that may lead to tumors in shorter-term studies in animals. Additionally, ARIKAYCE was not shown to be

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genotoxic in our standard series of tests. The relevance of the observed rat tumors to the use of ARIKAYCE in humans is not known.

In connection with the FDA's decision to lift the clinical hold for the CF *Pseudomonas aeruginosa* lung infection indication, we agreed to conduct a 9 month dog inhalation toxicity study of ARIKAYCE. In 2013, we concluded the 9 month dog inhalation toxicity study. In summary, the final report from the study stated that the lung macrophage response in dogs was similar to that seen in our previous 3 month dosing dog study, and there was no evidence of neoplasia, squamous metaplasia or proliferative changes.

We currently do not plan to initiate any further studies in *Pseudomonas* lung infections, except for our pediatric commitments.

Strategy for Commercialization

We believe ARIKAYCE will require a limited commercial infrastructure because of the center-based approach most widely used in the care of CF patients worldwide. We may seek to out-license ARIKAYCE in certain countries in Europe, as well as outside of Europe, Canada and the US.

INS1009 Inhaled Treprostinil for Pulmonary Arterial Hypertension

Disease

Pulmonary Arterial Hypertension, or PAH, is a chronic, life-threatening disorder characterized by abnormally high blood pressure in the arteries between the heart and lungs of an affected individual. PAH is one form of pulmonary hypertension. Pulmonary arteries carry blood from the heart to the lungs, where it picks up oxygen to be delivered throughout the body. In PAH, the pulmonary arteries constrict abnormally. This forces the heart to pump harder to maintain adequate blood flow which causes blood pressure within the lungs to rise. Common early symptoms include shortness of breath, fatigue, weakness, chest pain, and fainting, particularly during physical activity. PAH worsens over time and is life-threatening because the pressure in a patient's pulmonary arteries rises to dangerously high levels, putting a strain on the heart leading to heart failure.

Market and Current Treatment Options

There is no cure for PAH. PAH is estimated to have a prevalence of between 15 and 50 cases per 1 million adults and is considered an orphan disease.

Several medications are approved by FDA to treat symptoms:

- Treatment recommendations for early stage PAH include: diuretics, oxygen, anticoagulant, and digoxin therapy, as well as exercise.
- Advanced therapy includes treatment with endothelin receptor antagonists, phosphodiesterase 5 inhibitors and prostanoids.

The long term outcomes of medically treated patients remain uncertain, and transplantation remains an option for patients who fail on drug therapy. Prostanoid formulations used to treat PAH include intravenous epoprostenol (prostacyclin), intravenous treprostinil (a prostacyclin analog), subcutaneous treprostinil, inhaled treprostinil, oral treprostinil and inhaled iloprost. All prostanoid compounds have the limitation of a short half-life in the body, including treprostinil.

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For subcutaneous or intravenous administered treprostinil, continuous infusion is required and patients often experience injection site pain and increased risk of infection. Oral and inhaled forms of treprostinil require multiple dosing sessions per day with high and low cycling in blood levels. The initial high levels of drug may cause tolerability issues (cough, laryngeal irritation, emesis, hypotension and headache) and at the subsequent low levels of drug there may be reduced therapeutic benefit, especially in the overnight hours.

The current market for prostanoid therapies for PAH, including oral, IV and inhaled products, is in excess of $1 billion.

Current Program

INS1009. We believe that we can apply our proven design and development expertise to advance a new inhaled treatment that will address the current limitations of inhaled prostanoid therapies in PAH. We believe that our sustained-release inhaled treprostinil prodrug may prolong duration of effect and may provide greater consistency in pulmonary arterial pressure reduction over time. Current inhaled prostanoid therapies must be dosed four to nine times per day. Reducing dose frequency would therefore ease patient burden and may positively impact compliance. With our inhaled treprostinil prodrug that is released over time, we believe the potential for side effects due to initially high drug levels is reduced. For example, there may be reduced change in heart rate, change in blood pressure, and the severity and/or frequency of cough, as compared to treatment with current inhaled prostanoid therapies.

In late 2014, we completed a pre-IND meeting with the FDA for INS1009 and clarified that, subject to final review of the pre-clinical data, INS1009 could be eligible for a Section 505(b)(2) approval pathway. We are conducting preclinical work and toxicology evaluations related to the unique formulation and route of administration and, if results from these studies support our product concept, we may continue the program into development with the goal of submitting an IND application and commencing a phase 1 clinical study in the second half of 2015.

Strategy for Commercialization

We are constructing our development and commercialization plan for INS1009. We will evaluate independent development, co-development and out-licensing alternatives, as well as similar commercialization approaches.

ARIKAYCE for Non-CF Bronchiectasis Patients with *Pseudomonas* Lung Infections

Overview of Non-CF Bronchiectasis and Pseudomonas Lung Infections

Based on the positive results of a phase 2 placebo-controlled study in non-CF bronchiectasis, we believe ARIKAYCE has the potential to be used to treat non-CF bronchiectasis characterized by *Pseudomonas* lung infections. However, we are currently concentrating our development efforts on the treatment of patients with NTM lung infections and *Pseudomonas* lung infections in CF patients.

Non-CF bronchiectasis is a serious pulmonary condition characterized by localized, irreversible enlargement of the bronchial tubes. Accumulation of mucus in the bronchi leads to frequent infections, which causes inflammation and further reduces lung function. Patients evolve to a chronic inflammation-infection cycle. Disease burden has primarily been linked to productive cough and high levels of sputum production.

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Market

It is estimated that there are more than 250,000 non-CF bronchiectasis patients in the US (SDI Innovations in Healthcare Analytics, 2008), of which approximately 30% of non-CF bronchiectasis patients are infected with *Pseudomonas* (Wilson, C.B., et al., Eur Respir, 1997, 10(8):1754-1760); Nicotra, M.B., et al., Chest, 1995 108(4):955-961). Currently there are no approved antibiotics for this indication. When bronchiectasis patients become infected with *Pseudomonas*, they tend to have more frequent exacerbations and hospitalizations and are more frequent users of antibiotics.

Development Program

ARIKAYCE has been granted orphan drug status in the US for the treatment of bronchiectasis in patients with *Pseudomonas* and other susceptible microbial pathogens.

In May 2009 we completed our randomized, placebo controlled US phase 2 study (TR02-107) of ARIKAYCE in the treatment of chronic *Pseudomonas* infection in non-CF patients with bronchiectasis. In the study, 64 study subjects were randomized (1:1:1) to receive ARIKAYCE 280 mg, ARIKAYCE 560 mg or a placebo on a daily basis during a 28-day on-treatment period. The subjects completed follow-up assessments at the end of a 28-day off-treatment period. This study provided initial evidence of safety, tolerability and clinically meaningful improvement in pulmonary function throughout the on-treatment period in the treatment of chronic *Pseudomonas* infection in non-CF patients with bronchiectasis.

In the study both ARIKAYCE 280 mg and ARIKAYCE 560 mg were well tolerated. The adverse events experienced by patients during the study were consistent with underlying chronic lung disease in bronchiectasis patients. There was no evidence of renal toxicity or ototoxicity. Patients in the 560-mg cohort had a slightly higher frequency of dry cough post administration than patients in the 280 mg cohort. Cough was of short duration and self-limiting. One patient discontinued treatment due to dysphonia (hoarseness or difficulty speaking) and cough.

There was a statistically significant reduction in *Pseudomonas* density observed in the 560 mg ARIKAYCE cohort relative to the placebo cohort. Patients receiving ARIKAYCE experienced fewer pulmonary exacerbations at a rate of 4.7%, as compared to 10.5% in those receiving placebo. No patients in the ARIKAYCE cohorts required anti-*Pseudomonas* rescue treatment, whereas 15% of patients in the placebo cohort required treatment. Hospitalization from any cause occurred at a 5.3% rate for patients in the placebo cohort, as compared to a 2.3% rate for patients in the ARIKAYCE cohort. Patients receiving ARIKAYCE achieved improvements in patient respiratory symptoms and quality of life assessments compared with patients receiving placebo.

Although we believe there is an opportunity to develop ARIKAYCE for non-CF bronchiectasis, we currently do not intend to initiate further clinical studies with respect to a non-CF bronchiectasis indication.

IPLEX

In addition, we have another proprietary compound, IPLEX®, which is IGF-1, with its natural binding protein, IGFBP-3. IPLEX is no longer a development priority for us. We no longer have protein development capability or the in-house capability to manufacture IPLEX. Previously, under the proprietary IPLEX protein platform, we maintained an expanded access program for amyotrophic lateral sclerosis (also known as ALS or Lou Gehrig's disease) until drug supplies were exhausted at the end of 2011. It is our intention to seek licensing partners for the IPLEX development programs. In

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2012, we out-licensed the IPLEX technology to Premacure Holdings AB and Premacure AB of Sweden (collectively, Premacure) for retinopathy of prematurity indication. In March 2013, we amended the Premacure License Agreement to provide Premacure with the option to pay us $11.5 million and assume any of our royalty obligations to other parties in exchange for a fully paid license. In March 2013, Shire plc announced that they acquired Premacure. In April 2013 Shire exercised this option and paid us $11.5 million, and as a result we are not entitled to future royalties from Shire.

Manufacturing

ARIKAYCE Bulk Drug Substance

The ARIKAYCE used in our clinical studies is manufactured for us by Ajinomoto Althea, Inc. (Althea), a third-party contract manufacturing organization in the US. We are working with Althea to develop commercial production capabilities for ARIKAYCE. Our agreement with Althea expired on December 31, 2014. Althea is continuing to supply ARIKAYCE on a purchase order basis. We are negotiating a commercial supply agreement with Althea. There can be no assurance that we will enter into an agreement or that we will enter into an agreement on terms favorable to us.

In February 2014, we entered into a contract manufacturing agreement with Therapure for the manufacture of ARIKAYCE at the larger scales necessary to support commercialization. Pursuant to the agreement, the Company and Therapure are collaborating to construct a production area for the manufacture of ARIKAYCE in Therapure's existing manufacturing facility in Mississauga, Ontario, Canada. Therapure will manufacture ARIKAYCE for us on a non-exclusive basis. The agreement has an initial term of five years from the first date on which Therapure delivers ARIKAYCE to us after we obtain permits related to the manufacture of ARIKAYCE.

We are also exploring the possibility of establishing our own manufacturing facilities in order to support clinical studies and commercial supply of ARIKAYCE.

All sites of manufacture of ARIKAYCE use the technology developed and optimized by us. We and all our manufacturing partners must comply with applicable regulations relating to the current good manufacturing practices (cGMP) regulations of regulatory agencies. The cGMP regulations include requirements relating to the organization of personnel, buildings and facilities, equipment, control of components and drug product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports, and returned or salvaged products. We believe that all facilities will meet cGMP requirements for the sterile manufacturing of finished ARIKAYCE product.

Optimized eFlow Nebulizer System for ARIKAYCE

If approved for commercialization, we expect that ARIKAYCE will be administered once daily via inhalation using an eFlow Nebulizer System optimized specifically for ARIKAYCE by PARI, a third-party vendor.

The optimized eFlow Nebulizer System is a medical device that uses PARI's patented eFlow technology to enable highly efficient delivery of inhaled medication, also called aerosolization, including liposomal formulations via a vibrating, perforated membrane that includes thousands of specially designed laser-drilled holes, which aids the delivery of ARIKAYCE to the lung. We believe the optimized eFlow Nebulizer System is state of the art and highly efficient. The eFlow Nebulizer System delivers a very high density of active drug, in a precisely defined and controlled droplet size, with a high proportion of respirable droplets delivered in a relatively short period of time. In addition, the

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eFlow Nebulizer System has a quiet mode of operation, is small in size, light weight and provides for optional battery-powered operation. We believe that using the eFlow Nebulizer System to deliver ARIKAYCE will reduce treatment time and ease the patient's treatment burden and thereby potentially improve patient compliance. We believe that improved compliance with the prescribed treatment regimen may lead to a reduction in the development of antibiotic resistance by increasing the exposure of the infection to the minimum inhibitory concentration of antibiotic and therefore may ultimately lead to clinical benefit.

PARI manufactures eFlow nebulizer systems utilizing technology licensed, developed and optimized within its company and produces several commercially available eFlow technology based products for use in Europe, North America and other countries. PARI maintains facilities and equipment necessary to support manufacture of eFlow nebulizers for use with ARIKAYCE. PARI must comply with applicable governmental regulations relating to medical device production in each country of manufacture. We will continue to work with PARI to address our manufacturing needs for our clinical program. In July 2014, we entered into a commercialization agreement with PARI.

We seek to maintain the quality of our suppliers through quality agreements and our vendor audit program.

Intellectual Property

Patents and Trade Secrets ARIKAYCE

We own or license rights to more than 200 issued patents and pending patent applications in the US and in foreign countries, including more than 120 issued patents and pending patent applications related to ARIKAYCE. Our success depends in part on our ability to maintain proprietary protection surrounding our product candidates, technology and know-how; to operate without infringing the proprietary rights of others; and to prevent others from infringing our proprietary rights. We actively seek patent protection by filing patent applications, including both new inventions and improvements of existing technology that are important to the development of our business in the US, Europe, Canada and selected other foreign markets that we consider key for our product candidates. These international markets generally include Australia, Japan, China, India, Israel and Mexico.

Our patent strategy includes obtaining patent protection, where possible, on compositions of matter, methods of manufacture, methods of use, methods of treatment, dosing and administration regimens and formulations. We also rely on trade secrets, know-how, continuing technological innovation, in-licensing and partnership opportunities to develop and maintain our proprietary position.

We monitor for activities that may infringe our proprietary rights, as well as the progression of third-party patent applications that may have the potential to create blocks to our products or otherwise interfere with the development of our business. We are aware, for example, of U.S. patents, and corresponding international counterparts, owned by third parties that contain claims related to treating lung infections using inhaled antibiotics. If any of these patents were to be asserted against us, we do not believe that our proposed products would be found to infringe any valid claim of these patents.

Reflecting our commitment to safeguarding proprietary information, we require our employees, consultants, and collaborators to sign confidentiality agreements to protect the exchange of proprietary materials and information. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems.

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We own eight U.S. patents that, upon ARIKAYCE approval, would be listed in the FDA Orange Book that cover the ARIKAYCE composition and its use in treating lung infections, including *Pseudomonas* and NTM. These patents and their non-extended expiration dates are:

- U.S. Patent No. 7,544,369 (expires June 6, 2025),
- U.S. Patent No. 7,718,189 (expires June 6, 2025),
- U.S. Patent No. 8,226,975 (expires August 15, 2028),
- U.S. Patent No. 8,632,804 (expires December 5, 2026),
- U.S. Patent No. 8,802,137 (expires October 29, 2023),
- U.S. Patent No. 8,679,532 (expires December 5, 2026),
- U.S. Patent No. 8,642,075 (expires December 5, 2026), and
- U.S. Patent No. 8,673,348 (expires December 5, 2026).

We also own U.S. Patent No. 8,673,349 (expires December 5, 2026), which covers methods for treating a *Burkholderia* infection in a patient comprising administering to the patient an aerosolized composition comprising ARIKAYCE. In addition to our nine issued patents that cover ARIKAYCE composition and its use in treating lung infections, we own twelve pending U.S. patent applications that cover the ARIKAYCE composition, methods of using ARIKAYCE and methods for making ARIKAYCE.

Two patents have been granted by the European Patent Office ("EPO") (European Patent Nos. 1581236 and 1909759) and one additional patent application (Application No. 11159754.8) has been allowed. Currently, our European Patent No. 1909759 is being opposed by a third party. In addition, we have six applications pending before the EPO. Thirty nine patents have also issued in major foreign markets, e.g., Japan, China, Korea, Australia, and India, which cover ARIKAYCE and methods of using ARIKAYCE for treating lung infections. Forty five foreign patent applications are pending that cover the ARIKAYCE composition and its use in treating lung infections, including *Pseudomonas* and NTM. We anticipate that in the U.S., we will have potential patent coverage for ARIKAYCE and its use in treating lung infections, including *Pseudomonas* and NTM, through at least February 2029, which includes an additional six months of pediatric exclusivity.

Through our agreements with PARI, we have license rights to U.S. and foreign patents and applications that cover the eFlow Nebulizer System medical device. We have rights to use the nebulizers in clinical trials and we have entered into a commercial supply agreement with PARI.

Individual patents extend for varying time periods depending on the effective date of filing the patent application or the date of patent issuance, and the legal term of the patents in the countries in which they are obtained. Generally, patents issued in the US are effective for the longer of 17 years from the issue date or 20 years from the earliest effective filing date, if the patent application was filed prior to June 8, 1995; or 20 years from the earliest effective filing date, if the patent application was filed on or after June 8, 1995.

The term of our foreign patents varies in accordance with provisions of applicable local law, but typically is 20 years from the earliest effective filing date.

Patents and Trade Secrets INS1009

We own patent applications that if granted, would cover treprostinil analogs including INS1009, nanoparticle formulations of such treprostinil and prostacyclin analogs and methods for using such treprostinil analogs and nanoparticle formulations comprising the same in treating patients with

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pulmonary arterial hypertension and other diseases, as well as methods for manufacturing such prostacyclin analogs.

Trademarks

In addition to our patents and trade secrets, we have filed applications to register certain trademarks in the US and/or abroad, including INSMED, ARIKACE, ARIKAYCE, and IPLEX. At present, we have received either registration or a notice of allowance for these marks from the US Patent and Trademark Office. We have also received foreign allowances or issued foreign registrations for certain of these marks. In October 2013, we learned that the EMA had no objection to our use of the name ARIKAYCE. In early 2014, we learned that the FDA conditionally approved our use of the name ARIKAYCE as our proposed trade name for our liposomal amikacin for inhalation product candidate. Our ability to obtain and maintain trademark registrations will in certain geographical locations depend on making use of the mark in commerce on or in connection with our products and approval of the trademarks for our products by regulatory authorities in each country.

License and Collaboration Agreements

License Agreements and Other Collaboration Agreements Relating to ARIKAYCE

PARI Pharma GmbH We currently have a licensing agreement with PARI for use of the optimized eFlow Nebulizer System for delivery of ARIKAYCE in treating patients with NTM infections, CF and bronchiectasis. Under the licensing agreement, we have rights to several US and foreign issued patents, and patent applications involving improvements to the optimized eFlow Nebulizer System. We currently have rights to use the nebulizers in clinical trials and also entered into a commercial supply agreement with PARI.

We are obligated under this licensing agreement to use commercially reasonable efforts to develop, commercialize, market, and sell ARIKAYCE for use in CF indications in one or more countries (and at least in the US). Under the licensing agreement, we paid PARI an upfront license fee and PARI is entitled to receive milestone payments up to an aggregate of €4.3 million either in cash, qualified stock or a combination of both, at PARI's discretion, based on achievement of certain future milestone events including first acceptance of MAA submission (or equivalent) in the US of ARIKAYCE and the device, first receipt of marketing approval in the US for ARIKAYCE and the device, and first receipt of marketing approval in a major EU country for ARIKAYCE and the device. In addition, PARI is entitled to receive royalty payments in the mid-single digits on the net commercial sales of ARIKAYCE pursuant to the licensing agreement, subject to certain specified annual minimum royalties.

This license agreement will remain in effect on a country-by-country basis until the final royalty payments have been made with respect to the last country in which ARIKAYCE is sold, or until the agreement is otherwise terminated by either party. We have the right to terminate this license agreement upon written notice for PARI's uncured material breach, if PARI is the subject of specified bankruptcy or liquidation events, or if PARI fails to reach certain specified milestones. PARI has the right to terminate this license agreement upon written notice for our uncured material breach, if we are the subject of specified bankruptcy or liquidation events, if we assign or otherwise transfer the agreement to a third party that does not agree to assume all of our rights and obligations set forth in the agreement, or if we fail to reach certain specified milestones.

In July 2014, we entered into a Commercialization Agreement (the "PARI Agreement") with PARI for the manufacture and supply of eFlow nebulizer systems and related accessories (the

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"Device") as optimized for use with our proprietary liposomal amikacin for inhalation. The PARI Agreement has an initial term of fifteen years from the first commercial sale of the Device (the "Initial Term"). The term of the PARI Agreement may be extended by us for an additional five years by providing written notice to PARI at least one year prior to the expiration of the Initial Term.

Therapure Biopharma Inc. In February 2014, we entered into a Contract Manufacturing Agreement with Therapure for the manufacture of ARIKAYCE. Pursuant to the Agreement, we are collaborating with Therapure to construct a production area for the manufacture of ARIKAYCE in Therapure's existing manufacturing facility in Mississauga, Ontario, Canada. Therapure will manufacture ARIKAYCE for us on a non-exclusive basis. The agreement has an initial term of five years from the first date on which Therapure delivers ARIKAYCE to us after we obtain permits related to the manufacture of ARIKAYCE, and will renew automatically for successive periods of two years each, unless terminated by either party by providing the required two years' prior written notice to the other party. Notwithstanding the foregoing, the parties have rights and obligations under the agreement prior to the commencement of the initial term. The agreement allows for termination by either party upon the occurrence of certain events, including (i) the material breach by the other party of any provision of the agreement or the quality agreement expected to be entered into between the parties, or (ii) the default or bankruptcy of the other party. In addition, we may terminate the agreement for any reason upon no fewer than one hundred eighty days' advance notice. Costs incurred under this agreement will be recorded as a component of research and development expense until such time as we receive U.S. FDA approval for ARIKAYCE.

SynteractHCR, Inc. On December 30, 2014, we entered into Work Order 1 , pursuant to a Master Agreement for Services with SynteractHCR, Inc., ("Synteract"), dated as of August 27, 2014, as amended on December 23, 2014, pursuant to which we retained Synteract to perform implementation and management services in connection with certain clinical trials pursuant to a specific protocol of pharmaceutical products under development by us or under our control. Synteract is providing comprehensive services for the 212 study. Prior to the execution of the Work Order, Synteract was providing such services pursuant to a Letter of Intent, dated August 25, 2014. The Work Order covers services related to the 212 study only and any additional study or services will be subject to the negotiation and execution of an additional work order. It is anticipated that aggregate costs to us relating to the Work Order will be approximately $33 million over the period of the study.

Cystic Fibrosis Foundation Therapeutics, Inc. In 2005 and 2009, we entered into research funding agreements with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) whereby we received $1.7 million and $2.2 million for each respective agreement in research funding for the development of ARIKAYCE. If ARIKAYCE becomes an approved product for CF in the US, we will owe a payment to CFFT of up to $13.4 million that is payable over a three-year period after approval as a commercialized drug in the US. Furthermore, if certain global sales milestones are met within 5 years of the drug commercialization, we would owe an additional payment of $3.9 million.

National Institutes of Allergy and Infectious Diseases In 2012, we entered into a cooperative research and development agreement (CRADA) with National Institutes of Allergy and Infectious Diseases (NIAID) to evaluate the safety and efficacy of ARIKAYCE in patients with NTM lung disease in our phase 2 clinical study. NIAID agreed to provide biostatistical advisory input in connection with the phase 2 NTM study. If we decide not to continue with the commercialization of ARIKAYCE in NTM, NIAID will have the right to complete the clinical trial. Further NIAID may elect to pursue its rights to obtain license rights to certain inventions made under the CRADA.

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License Agreements and Other Collaboration Agreements Relating to Other Compounds

Ipsen and Genentech In March 2007, we were granted a license or sublicense as applicable to patents held by Ipsen and Genentech to develop IPLEX in certain medical indications in the US and foreign territories. In November 2008 we gained Royalty-Free Worldwide Rights for IPLEX from Ipsen and Genentech in connection with potential expanded access ALS programs.

NAPO Pharmaceuticals In January 2007, we entered into an agreement with NAPO Pharmaceuticals, whereby we granted NAPO a license for INSM-18 also known as Masoprocal. The license gives NAPO the right to develop, manufacture and commercialize Masoprocal products for any indications relating specifically to diabetes, cardiac disease, vascular disease, metabolic disease and Syndrome X. The agreement calls for payments from NAPO to us upon the achievement of certain milestones which have not yet been met.

TriAct In December 2010, we entered into an agreement with TriAct Therapeutics Inc. ("TriAct") whereby we granted TriAct an exclusive license for INS-18 also known as Masoprocal. The license gives TriAct the right to develop, manufacture and commercialize Masoprocal products for any indications relating specifically to oncology. The agreement calls for the issue of TriAct common stock to Insmed upon the achievement of certain milestones. To date, no milestones have been achieved and no common stock has been received.

Eleison In February 2011, we entered into an agreement with Eleison Pharmaceuticals whereby we granted Eleison an exclusive license for Inhaled CISPLATIN Lipid Complex. The license gives Eleison the right to develop, manufacture and commercialize inhaled CISPLATIN Lipid Complex for cancers affecting the lung. Payments totaling $1.0 million were received in 2011 and were recorded in license fees.

Premacure (now Shire plc) In May 2012, we entered into an agreement with Premacure pursuant to which we granted to Premacure an exclusive, worldwide license to develop manufacture and commercialize IGF-1, with its natural binding protein, IGFBP-3, for the prevention and treatment of complications of preterm birth (the "Premacure License Agreement"). In March 2013, we amended the Premacure License Agreement to provide Premacure with the option to pay us $11.5 million and assume any of our royalty obligations to other parties in exchange for a fully paid license. In March 2013, Shire plc announced that they acquired Premacure. In April 2013 Shire exercised this option and paid us $11.5 million, and as a result we are not entitled to future royalties from Shire.

Competition

The biotechnology and pharmaceutical industries are highly competitive. We face potential competitors from many different areas including commercial pharmaceutical, biotech and device companies, academic institutions and scientists, other smaller or earlier stage companies and non-profit organizations developing anti-infective drugs and drugs for respiratory diseases. Many of these companies have greater human and financial resources and may have product candidates in more advanced stages of development and may reach the market before our product candidates. Competitors may develop products that are more effective, safer or less expensive or that have better tolerability or convenience. We also may face generic competitors where third-party payers will encourage use of the generic products. Although we believe that our formulation delivery technology, respiratory and anti-infective expertise, experience and knowledge in our specific areas of focus provide us with competitive advantages, these potential competitors could reduce our commercial opportunity.

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Major Competitors for ARIKAYCE

Our major competitors include pharmaceutical and biotechnology companies that have approved therapies or therapies in development for the treatment of chronic lung infections. There are no approved therapies for NTM in the United States or Europe. While there is no approved treatment for NTM lung infections, there is an American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) treatment regimen that is utilized.

Inhaled antibiotics are a standard of care in the treatment of CF to manage the chronic *Pseudomonas* infections due to the high concentrations of drug deposited directly into the lung, where the infection resides.

Novartis has two products for the treatment of *Pseudomonas* lung infections in CF patients. Tobi inhaled solution was the first inhaled antibiotic to be approved by the FDA for the treatment of CF patients with *Pseudomonas* lung infections and has been sold in the US since January 1998. Tobi inhaled solution requires administration twice daily for approximately 15 to 20 minutes per treatment for a daily total of approximately 30 to 40 minutes per day. Tobramycin inhalation powder, also known as TIP or Tobi Podhaler®, is a dry powder version of tobramycin approved by the EMA in 2011 and FDA in 2013 for use by CF patients with *Pseudomonas*. TIP requires administration twice daily for approximately 5 to 10 minutes per treatment for a daily total of 10 to 20 minutes per day. The Tobi products continue to be the most used products in Europe and the US.

Actavis plc ("Actavis") markets inhaled colistin in Europe under the name Colomycin® as inhaled solution and Colobreathe as inhaled dry powder. Colistin is used in Europe primarily as an adjunct therapy and in some cases as a primary therapy. Because it is less expensive than Tobi, colistin is used as a first line treatment in some countries that have a more restrictive reimbursement system. Colistin is not approved for inhaled treatment in the US, but it is frequently used off label (via pharmacist compounding) for patients that cannot use Tobi and for more severe patients in the off month alternating with Tobi in an attempt to maintain lung function in patients who are deteriorating on Tobi alone.

Gilead Sciences markets Cayston® (aztreonam for inhalation) which received approval from the FDA in early 2010. Cayston requires administration three times per day for two to three minutes for each treatment for a daily total of approximately about 10 minutes. Gilead received conditional approval for Cayston in Europe during September 2009. Cayston is approved for one cycle of treatment.

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Market data on marketed competitors for the treatment of *Pseudomonas* lung infections in CF patients as reported by the individual companies is summarized below:

Competitor	Product/Product Candidate for Pseudomonas Lung Infections in CF Patients	Class of Product	Key Marketing Approvals	Estimated Annual Sales (millions)
Novartis	Tobi (Tobramycin Inhalation Solution or TIS)	Aminoglycoside	Europe, US and Canada	$281 (combined)
Novartis	Tobi Podhaler (Tobramycin Inhalation Powder or TIP)	Aminoglycoside	Europe, US and Canada	
Gilead	Cayston (Aztreonam for Inhalation Solution)	Monobactam	Europe and US	Not reported
Actavis	Colomycin (Colistimethate Sodium for Inhalation)	Polymyxin	Europe	Not reported
Actavis	Colobreathe (Colistimethate Sodium Powder)	Polymyxin	Europe	Not reported
Chiesi	Bramitob® and BETHKIS (Tobramycin Inhalation Solution)	Aminoglycoside	Europe and US	Not reported
Actavis	Aeroquin (Inhaled Levofloxacin)	Flouroquinolone	None phase 3 (data reported)	Not approved

Major Competitors for INS1009 (PAH)

In addition to major competitors, there are additional investigational therapies for pulmonary arterial hypertension being developed by both large and small pharmaceutical, biotechnology and other companies. Relative to us, many of these entities have substantially greater capital resources, research and development staffs, facilities and experience in conducting clinical studies and obtaining regulatory approvals, as well as in manufacturing and marketing pharmaceutical products.

Market data on marketed competitors for the treatment of PAH as reported by the individual companies is summarized below:

Competitor	Product/Product Candidate for PAH	Class of Product	Key Marketing Approvals	Estimated Annual Sales (millions)
United Therapeutics	Tyvaso (treprostinil) Inhalation Solution	Prostacyclin analogue	US	$463
United Therapeutics	Orenitram (treprostinil) Extended-release tablets	Prostacyclin analogue	US	$41
United Therapeutics	Remodulin (treprostinil) Injection	Prostacyclin analogue	US, Europe and Canada	$554
Actelion / Bayer	Ventavis (iloprost) Inhalation Solution	Prostacyclin analogue	US (Actelion) / Europe and Australia (Bayer)	CHF 110 (US, 2013) Ex-US not reported
Actelion	Uptravi (selexipag) film-coated tablets	Prostacyclin analogue	None (filed in US and Europe)	Not approved

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Government Regulation

Orphan Drugs

European Union

The European Commission grants orphan drug designation to promote the development of products that may offer therapeutic benefits for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the EU. Orphan drug designation can also be granted if the drug is intended for a life threatening, seriously debilitating or serious and chronic condition in the EU and without incentives sales of the drug in the EU are likely to be sufficient to justify developing the drug. Orphan drug designation is available either if there is no other satisfactory method approved in the EU of diagnosing, preventing or treating the condition or if such a method does exist but the proposed orphan drug will be of significant benefit to patients.

Orphan drug designation provides opportunities for free protocol assistance and fee reductions for access to the centralized regulatory procedures before and during the first year after marketing approval, which reductions however are not limited to the first year after marketing approval for small and medium enterprises. In addition, if a product which has an orphan drug designation subsequently receives a marketing authorization for a therapeutic indication which is covered by such designation, the drug is entitled to orphan drug exclusivity, which means the EMA or national Medicines Agency may not accept another application for the authorization, or grant an authorization, for a similar drug for the same therapeutic indication for a period of ten years. Each orphan designation carries the potential for one market exclusivity for all the therapeutic indications that are covered by the designation. A product that has several separate orphan designations has several separate market exclusivities. The period of market exclusivity is extended by two years where an agreed pediatric investigation plan has been implemented (see Pediatric Information section below).

The exclusivity period may be reduced to six years if the designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Competitors may receive a marketing authorization for similar drugs or biologics for the same indication(s) for which the orphan product has exclusivity. In order to do so, however, they must demonstrate that the existing orphan product is not supplied in sufficient quantities or that the 'second' drugs or biologics are clinically superior to the existing orphan product. The 'second' drug may not need to have an orphan designation as well; insufficient supplies or clinical superiority allows a competitor to obtain a marketing authorization but does not trigger an orphan designation.

United States

Under the Orphan Drug Act (ODA), the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition ("rare" generally meaning that it affects fewer than 200,000 individuals in the US) if it meets certain criteria specified in the ODA and FDA's implementing regulations at 21 CFR Part 316. After the FDA grants orphan drug designation, the generic identity of the drug and the specific potential uses for which it has obtained designation are made publicly available by the FDA.

Orphan drug designation qualifies the drug sponsor for various development incentives of the ODA, including tax credits for qualified clinical testing, and a waiver of the NDA application user fee (unless the application includes an indication for other than the rare disease or condition for which the drug was designated). It also provides the potential for certain exclusivity benefits. However, it does not

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alter the timing or scope of the regulatory review and approval process; safety and effectiveness of a drug must still be established through adequate and well-controlled studies. The first NDA applicant with FDA orphan drug designation for a particular active ingredient to receive FDA approval of the drug for an indication covered by the orphan designation is entitled to a seven-year exclusive marketing period, often referred to as orphan drug exclusivity, in the US for that product and indication. During the orphan drug exclusivity period, the FDA may not approve any other applications to market the same drug for the same indication for use, except in limited circumstances, such as a showing of clinical superiority to the product that has orphan drug exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition.

Drug Approval

European Union

Marketing Authorization Application

To obtain approval of a drug under EU regulatory systems, an application for a marketing authorization may be submitted under a centralized, a decentralized or a national procedure. These procedures apply in the European Economic Area, i.e. the EU member states plus the three EFTA countries, (Iceland, Lichtenstein, and Norway). The centralized procedure, which is compulsory for medicines produced by certain biotechnological processes and for orphan drugs provides for the grant of a single marketing authorization that is valid for all EU member states and the three EFTA countries, which grants the same rights and obligations in each member state or EFTA country as a national marketing authorization. As a general rule, only one marketing authorization may be granted for drugs approved through the centralized procedure.

Under the centralized procedure, the EMA's Committee for Human Medicinal Products for Human Use (CHMP) is required to adopt an opinion on a valid application within 210 days, excluding clock stops, when additional information is to be provided by the applicant in response to questions. More specifically, on day 120 of the procedure, once the CHMP has received the preliminary assessment reports and opinions from the Rapporteur and Co-Rapporteur, it prepares a list of potential outstanding issues, which are sent to the applicant together with the CHMP's recommendation. Applicants then have three months to respond to the CHMP (and can request a three-month extension). The Rapporteur and Co-Rapporteur assess the applicant's replies, submit them for discussion to the CHMP and prepare a final assessment report. Once its scientific evaluation is completed, the CHMP gives a favorable or unfavorable opinion as to whether to grant the marketing authorization. After the adoption of the CHMP opinion, a decision on the MAA must be adopted by the European Commission, after consulting the Standing Committee of the Member States. The European commission prepares a draft decision and circulates it to the member states; if the draft decision differs from the CHMP opinion, the Commission must provide detailed explanations. The Commission adopts a decision within 15 days of the end of the consultation procedure.

Fast Track Review, Conditional Approval and Approval Under Exceptional Circumstances

Various programs, including fast track review, conditional approval and approval under exceptional circumstances, are intended to expedite or simplify the approval of drugs that meet certain qualifications. The purpose of these programs is to provide important new drugs to patients earlier than under standard approval procedures.

For drugs or biologics which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, applicants may submit a substantiated request for accelerated assessment. If the CHMP accepts the request, the review time is reduced to 150 days.

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Furthermore, for certain categories of medicinal products, it may be necessary to grant marketing authorizations on the basis of less complete data than is normally required in order to meet unmet medical needs of patients and in the interest of public health. In such cases, it is possible for the CHMP to recommend the granting of a marketing authorization, subject however to certain specific obligations to be reviewed annually; such marketing authorization may be conditional or under exceptional circumstances. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization or marketing authorization under exceptional circumstances. The granting of conditional marketing authorization or marketing authorization under exceptional circumstances will depend on the applicant's ability to fulfill the conditions imposed within the agreed upon deadline.

Conditional marketing authorizations may be granted for products designated as orphan medicinal products, if all of the following conditions are met: (1) the risk-benefit balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) the product fulfills unmet medical needs, and (4) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Conditional marketing authorizations are valid for one year, on a renewable basis until the holder provides a comprehensive data package. The holder will be required to complete ongoing studies or to conduct new studies with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data. Once the holder has provided a comprehensive data package, the conditional marketing authorization is replaced by a 'regular' marketing authorization.

Marketing authorizations under exceptional circumstances may be granted where the applicant demonstrates that, for objective and verifiable reasons, he is unable to provide comprehensive data on the efficacy and safety of the drug under normal conditions of use. Such marketing authorizations are subject to certain conditions, in particular relating to safety of the drug, notification of incidents relating to its use or actions to be taken. They are valid for an indefinite period of time, but the conditions upon which they are based are subject to an annual reassessment.

United States

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. The Federal Food, Drug, and Cosmetic Act (FDCA) and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling and import and export of pharmaceutical products. Failure to comply with applicable US requirements at any time during the product development process, approval process or after approval may subject a company to a variety of administrative or judicial sanctions, such as imposition of clinical holds, FDA refusal to approve and even accept for review pending new drug applications, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement, civil penalties, and criminal prosecution.

Pharmaceutical product development in the US may include:

- Completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;

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- Submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin;
- Approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- Performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug for each indication;
- Submission to the FDA of a 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.

Adequate and well-controlled clinical trials must be conducted to establish the safety and effectiveness of the drug for each indication for which FDA approval is sought. In certain cases, FDA may approve a drug based on one clinical study plus confirmatory evidence. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease.

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, formulation and toxicity, pharmacology, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements including FDA's good laboratory practices regulations and USDA's regulations implementing Animal Welfare Act. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature, and a proposed clinical trial protocol, among other things, to the FDA as part of an IND. Certain non-clinical tests, such as animal tests of reproductive toxicity and carcinogenicity, 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 clinical 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 human subjects (healthy volunteers or patients) under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with good clinical practice, or GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing to be conducted in the U.S. (patients and healthy volunteers), as well as 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 generally 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, or NIH, for public dissemination on their ClinicalTrials.gov website.

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Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and there are additional, more frequent reporting requirements for suspected serious adverse reactions.

A study sponsor might choose to discontinue a clinical trial or a clinical development program for a variety of reasons. The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial subjects. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap or be combined. For phase 1, the initial introduction of the drug into healthy human subjects or patients with the target disease or condition, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses and, if possible, early evidence on effectiveness. Phase 2 usually involves trials in a limited patient population with the target disease or condition 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. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in phase 2 evaluations, phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, in order to generate enough data to statistically evaluate the drug for potential approval, to establish the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug.

In some cases, FDA may condition approval of a NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials to further assess the drug's safety and effectiveness after NDA approval. Such post-approval trials are typically referred to as phase 4 studies. In some circumstances, the FDA may also order a sponsor to conduct post-marketing clinical trials after approval of the product, if new safety information arises raising questions about the drug's risk-benefit profile. Those clinical trials are typically referred to as Post-Marketing Requirements, or PMRs.

NDA Application

After completion of the required clinical testing, an NDA is prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the US. The NDA must include the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls. The cost of preparing and submitting an NDA is substantial. Under federal law, the submission of most NDAs is additionally subject to a substantial application user fee, and the manufacturer and/or sponsor under an approved new drug application are also subject to annual product and establishment user fees. These fees are typically increased annually.

The FDA has 60 days from its receipt of a NDA to determine whether the application will be accepted for filing based on the FDA's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Under Prescription Drug User Fee Act guidelines that are currently in effect, the FDA has a goal of twelve months from the date of the receipt of a standard nonpriority NDA to review and act on the submission for a drug considered to be a new molecular entity, or eight months for a priority NDA for such drug. The review process

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may be extended by FDA for three additional months to consider certain information or clarification regarding information already provided in the submission.

The FDA may refer applications for novel drug products or drug products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

Before approving a NDA, the FDA will typically inspect one or more clinical sites to assure compliance with Good Clinical Practice. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. FDA will not approve the product unless compliance with current good manufacturing practices is satisfactory and the NDA contains data that provide substantial evidence that the drug is safe and effective in the indication studied.

After the FDA evaluates the NDA and the manufacturing and testing facilities, it issues either an approval letter or a complete response letter. Complete response letters generally outline the deficiencies in the submission and delineate the additional testing or information needed in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy and may impose other conditions, including labeling restrictions that can materially affect the potential market and profitability of the drug. The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, plan to mitigate any identified or suspected serious risks. The REMS 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. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Market and data exclusivity provisions under the FDCA can delay the submission or the approval of certain applications for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of a NDA for a new chemical entity (also referred to as "NCE"). 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 for a new chemical entity, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company that references the previously approved drug. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement.

The FDCA also provides three years of marketing exclusivity for a NDA, 505(b)(2) NDA, or supplement to an existing NDA or 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

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ANDAs or 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.

After NDA approval, owners of relevant drug patents may apply for up to a five-year patent extension. The allowable patent term extension is calculated as half of the drug's testing phase (the time between IND application and NDA submission) and all of the review phase (the time between NDA submission and approval) up to a maximum of five years. The time can be shortened if FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years. For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the United States Patent and Trademark Office must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which a NDA has not been submitted.

The Subpart H regulations allow certain drugs, for serious or life-threatening conditions, to be approved on the basis of surrogate endpoints or clinical endpoints other than survival or irreversible morbidity. As a condition of approval under Subpart H, the FDA may require certain adequate and well-controlled post-marketing clinical studies to verify and describe clinical benefit of the product as well as fulfill certain other post-marketing commitments. If the required post-marketing studies fail to verify the clinical benefit of the drug, or if the applicant fails to perform the required post-marketing studies with due diligence, the FDA may withdraw approval of the drug following a hearing conducted under the agency's regulations. Under Subpart H, the agency may also withdraw approval of a drug if, among other things, the promotional materials for the product are false or misleading, or other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

Breakthrough Designation, Fast Track Designation and Priority Review

The FDA has various programs, including breakthrough designation, fast track designation and priority review that are intended to expedite or simplify the process for the development and FDA review of drugs that meet certain qualifications. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

In July 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed. FDASIA provides for a new designation Breakthrough Therapy Designation. A breakthrough therapy is a drug intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. If a drug is designated as breakthrough therapy, FDA will expedite the development and review of such drug.

Increasing rates of bacterial and fungal infections and resistance to current therapies, along with associated high rates of mortality, led to the 2012 passage of the Generating Antibiotic Incentives Now (GAIN) Act in the United States. The GAIN Act established incentives for the development of new therapies for serious and life-threatening infections by making streamlined priority review and fast track processes available for drugs which the FDA designates as Qualified Infectious Disease Products,

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or QIDPs. To qualify for designation as a QIDP according to the criteria established in the GAIN Act a product must be an antibacterial or anti-fungal drug for human use intended to treat serious or life-threatening infections, including: those caused by an anti-fungal resistant pathogen, including novel or emerging infectious pathogens; or caused by qualifying pathogens listed by the FDA in accordance with the GAIN Act.

Under the fast track program generally, the sponsor of an IND may request FDA to designate the drug candidate as a fast track drug if it is intended to treat a serious condition and fulfill an unmet medical need. FDA must determine if the drug candidate qualifies for fast track designation within 60 days of receipt of the sponsor's request. Once FDA designates a drug as a fast track candidate, it is required to facilitate the development and expedite the review of that drug by providing more frequent communication with and guidance to the sponsor.

In addition to other benefits such as the ability to have more interactions with FDA, FDA may initiate review of sections of a fast track drug's NDA before the application is complete. This rolling review is available if the applicant provides and FDA approves a schedule for the submission of the remaining information and the applicant pays applicable user fees. However, FDA's time period goal for reviewing an application does not begin until the last section of the NDA is submitted. Additionally, the fast track designation may be withdrawn by FDA if FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

Under FDA policies, a drug candidate is generally eligible for priority review, or review within an eight-month time frame from the time an NDA is submitted, if the drug candidate provides a significant improvement compared to marketed drugs in the treatment, diagnosis or prevention of a disease. A fast track designated drug candidate would ordinarily meet FDA's criteria for priority review. The FDA makes its determination of priority or standard review during the 60-day filing period after a NDA submission, and the GAIN Act establishes priority review for QIDPs.

Combination Products

A combination product is a product comprised of (i) two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (ii) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (iii) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (iv) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

FDA is divided into various branches, or Centers, by product type. Different Centers typically review drug, biologic, or device applications. In order to review an application for a combination product, the FDA must decide which Center should be responsible for the review. FDA regulations require that FDA determine the combination product's primary mode of action, or PMOA, which is the single mode of a combination product that provides the most important therapeutic action of the combination product. The Center that regulates that portion of the product that generates the PMOA becomes the lead evaluator. If there are two independent modes of action, neither of which is

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subordinate to the other, the FDA makes a determination as to which Center to assign the product based on consistency with other combination products raising similar types of safety and effectiveness questions or to the Center with the most expertise in evaluating the most significant safety and effectiveness questions raised by the combination product. When evaluating an application, a lead Center may consult other Centers and apply the standards that would be applicable but still retain complete reviewing authority, or it may collaborate with another Center, by which the Center assigns review of a specific section of the application to another Center, delegating its review authority for that section. Typically, the FDA requires a single marketing application submitted to the Center selected to be the lead evaluator, although the agency has the discretion to require separate applications to more than one Center. One reason to submit multiple evaluations is if the applicant wishes to receive some benefit that accrues only from approval under a particular type of application, like new drug product exclusivity. If multiple applications are submitted, each may be evaluated by a different lead Center.

Like their constituent products drugs and devices combination products are highly regulated and subject to a broad range of post marketing requirements including cGMPs, adverse event reporting, periodic reports, labeling and advertising requirements and restrictions.

Antibiotic Exclusivity

If FDA designates a drug product as a QIDP, and if that product is approved, FDA will extend by an additional five years any non-patent marketing exclusivity period awarded, such as a five-year exclusivity period awarded for a new chemical entity or a seven-year exclusivity period awarded for an approved product with orphan designation. For example, an approved product with orphan designation and QIDP designation would have twelve years of marketing exclusivity. This exclusivity applies only with respect to drugs that are first approved on or after July 9, 2012.

A drug sponsor may request that FDA designate its product as a QIDP at any time prior to NDA submission. FDA must make a QIDP determination within 60 days of receiving the designation request. Any NDA for a drug designated as a QIDP will be granted priority review.

Disclosure of Clinical Trial Information

Under U.S. and certain foreign laws intended to improve clinical trial transparency sponsors of clinical trials are in many cases required to register and disclose information about their clinical trials. This can include information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated in many cases to disclose the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved. Competitors may use this publicly-available information to gain knowledge regarding the progress of development programs.

Other US Post marketing Regulatory Requirements

Once an NDA is approved, a product will be subject to certain post-approval requirements. For instance, FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the Internet.

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Drugs may be marketed only for the approved indications and in accordance with the provisions of the approved labeling. Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. A NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Adverse event reporting and submission of periodic reports is required following FDA approval of a NDA. The FDA also may require post market studies, known as phase 4 studies, and may require a REMS, which could restrict the distribution or use of the product.

In addition, quality control as well as drug manufacture, packaging, and labeling procedures must continue to conform to cGMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA during which the FDA inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMPs.

Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered.

In addition to the potential post marketing commitments and requirements noted above (for example, phase 4 studies, REMS) drugs manufactured or distributed pursuant to FDA approvals are subject to post market requirements, including those relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, many 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.

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 for compliance with cGMP and other 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 time, money, and effort in the area of production and quality control to maintain cGMP compliance. FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained, if problems occur after the product reaches the market or if required phase 4 studies do not demonstrate efficacy.

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

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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;
- 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 in accordance with the provisions of the approved indication and labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion for uses not consistent with the approved labeling, and a company that is found to have improperly promoted off-label uses may be subject to significant liability under both the FDCA and other statutes, including the False Claims Act.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Pediatric Information

European Union

In the European Union, new drugs (i.e. drugs containing a new active substance) for adults, must also be tested in children. This mandatory pediatric testing is carried out through the implementation of a pediatric investigation plan, or PIP, which is proposed by the applicant and approved by the EMA. A PIP contains all the studies to be conducted and measures to be taken in order to support the approval of the new drug, including pediatric pharmaceutical forms, in all subsets of the pediatric population. Validation of the marketing authorization application for adults is subject to the implementation of the PIP. However, one the one hand, the PIP may allow a deferral for one or more of the studies or measures included therein in order not to delay the approval of the drug in adults, and, on another hand, the EMA may grant either a product-specific waiver for the (adult) disease/condition or one or more pediatric subsets or a class waiver for the disease/condition. PIPs are subject to modifications from time to time, when they no longer are workable. Prior to obtaining the validation of a marketing authorization application for adults, the applicant has to demonstrate compliance with PIP at the time of submission of the application. In the case of orphan medicinal products, completion of an approved PIP can result in an extension of the market exclusivity period from ten to twelve years.

In December 2010, the EMA agreed on our PIP, on the granting of a deferral, and on the granting of a waiver for amikacin (sulfate) nebulizer suspension for inhalation use, in the treatment of *Pseudomonas* lung infection/colonization in CF patients in accordance with relevant European regulations. A modification of the PIP was submitted in connection with our MAA filing, which was validated by the EMA in February 2015.

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United States

Under the Pediatric Research Equity Act of 2003, or PREA, NDAs and NDA supplements must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of an applicant, grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted. Under the Best Pharmaceuticals for Children Act (BPCA), pediatric research is incentivized by the possibility of six additional months of pediatric exclusivity, which if granted, is added to existing exclusivity periods and patent terms listed for the applicable drug in the FDA's Orange Book at the time the sponsor satisfies FDA's "written request" for pediatric research. Sponsors may negotiate the terms of the written request during drug development. While the sponsor of an orphan designated drug may not be required to perform pediatric studies under PREA, they are eligible to participate in the incentives under the BPCA.

Regulation Outside the US and Europe

In addition to regulations in the US and Europe, we will be subject to a variety of regulations in other jurisdictions governing clinical studies of our candidate products. Whether or not we obtain FDA approval for a product, we must obtain approval of a product by the comparable regulatory authorities of countries outside the US before we can commence clinical studies or marketing of the product in those countries. The requirements for approval and the approval process vary from country to country, and the time may be longer or shorter than that required for FDA approval. Furthermore, we must obtain any required pricing approvals in addition to regulatory approval prior to launching the product in the approving country.

Health Canada

Health Canada (HC) is the government agency that provides regulatory and marketing approval for drugs and therapeutic products in Canada. The upcoming Legislative and Regulatory Modernization (LRM) is the most significant drug regulatory system reform in Canada in more than 50 years and is expected to overhaul Canada's Food and Drugs Act and Regulations. The LRM supports a 'lifecycle' regulatory approach and is focused on strengthening evidence-based decision making, good regulatory planning, licensing, post-licensing, accountability, authority and enforcement. Through this framework, HC intends to improve the market authorization process and implement necessary regulatory frameworks. In October 2010, HC accelerated its modernization efforts. This included the proposed regulatory pathways for Orphan Drugs (harmonized with US/EU regulations).

Japan

The Minister of Health, Labour and Welfare is the government agency that provides regulatory approval for pharmaceutical products in Japan. Parties engaged in manufacture or sale of products in Japan must receive the approval of the Minister of Health, Labour and Welfare. The Pharmaceutical Affairs Law of Japan requires a license for marketing authorization when importing to Japan and selling pharmaceutical products manufactured in other countries. It also requires a foreign manufacturer to get each of its manufacturing sites certified as a manufacturing site of pharmaceutical products to be marketed in Japan. To receive a license for marketing authorization, the manufacturer or seller must, at the very least, employ the certain manufacturing marketing, quality and safety personnel. A license for marketing authorization may not be granted if the quality management methods and post marketing safety management methods applied with respect to the pharmaceutical

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product fail to conform to the standards stipulated in the ordinances promulgated by the Ministry of Health, Labour and Welfare.

In addition to the licensing requirements for entities that engage in manufacturing, importing and sales of medical products as mentioned above, the law also requires that the medical products have obtained approval before they are marketed and sold in Japan. The process for the approval includes such elements as evaluation and testing of trustworthiness of the clinical trial, testing of quality, efficacy, absorption and egestion, toxicity, and safety of the products. The time required for the approval process varies depending on the product, but it can be years. The product also needs approval for pricing to be applied for redemption of health insurance. The medical products which once are approved and marketed are also subject to regular post-marketing vigilance of safety and quality under the standards of Good Manufacturing Practice.

Australia

The Therapeutic Goods Administration ("TGA") is the regulatory body, under the Australian Department of Health, responsible for conducting assessment and monitoring activities of therapeutic goods in Australia. Products under the jurisdiction of the TGA include prescription medicines, medical devices (simple and complex), diagnostic products, vaccines, and biologics. Activities of the TGA include classifying the product based on risk to the person, implementing appropriate regulatory controls for the manufacturing processes, and monitoring approved products with a comprehensive adverse event reporting program. The TGA requires that a marketing authorization be submitted and reviewed for safety and efficacy, and approved before a medication can be marketed and provided to patients commercially. A separate regulatory pathway is utilized to conduct clinical trials in Australia. Australia has also an Orphan drug designation.

Medical Device Regulation

If approved, ARIKAYCE will be administered via inhalation through an optimized eFlow Nebulizer System, which is a medical device that is also subject to extensive government regulation. The optimized eFlow Nebulizer System is approved in the EU, and it must be approved in any country in which we intend to commercialize ARIKAYCE.

Medical devices may seek and receive marketing authorization from FDA as stand-alone devices, or in some cases, may seek and receive marketing authorization as part of a combination product. In either case, the ultimate product will need to satisfy FDA requirements. The basic pathways for marketing authorization for devices in the United States are 510(k) clearance.

Medical devices are also subject to certain post-clearance, post-approval requirements. Those requirements include continuing Quality System Regulation compliance, Medical Device Reporting, Correction and Removal, and requirements governing labeling and promotional advertising.

In addition to regulations in the US, we will be subject to a variety of regulations in other jurisdictions governing the medical device. Whether or not we obtain FDA approval for a product and the medical device that will be used with ARIKAYCE, we must obtain approval of a product and the medical device by the comparable regulatory authorities of countries outside the US before we can commence marketing of the product in those countries. The requirements for approval and the approval process vary from country to country, and the time may be longer or shorter than that required for FDA approval.

Under certain harmonized medical device approval/clearance regulations outside the US, reference to US clearance permits fast-tracking of market clearance. Other regions are harmonized

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with EU standards, and therefore recognize the CE mark (Conformité Européene, which means European Conformity) as a declaration of conformity to applicable standards. CE mark is standard designation for EU member States for market authorization.

Early Access Programs

European Union

Under European law, member states are authorized to adopt national legal regimes for the supply or use of non-authorized drugs in case of therapeutic needs. The most common national legal regimes are compassionate use programs and named patient sales, but other national regimes for early access may be available, depending on the member state. For drugs approved through the centralised procedure, such as orphan drugs, compassionate use programs are also regulated at the European level.

Special programs can be set up to make available to patients with an unmet medical need a promising medicine which has not yet been authorized for their condition ("compassionate use"). As a general rule, compassionate use programs can only be put in place for drugs or biologics that are expected to help patients with life-threatening, long-lasting or seriously disabling illnesses. These programs are expected to benefit seriously ill patients who currently cannot be treated satisfactorily with authorized medicines, or who have a disease for which no medicine has yet been authorized. The compassionate use route may be a way for patients who cannot enroll in an ongoing clinical trial to obtain treatment with a potentially life-saving medicine. Compassionate use programs are coordinated and implemented by the EU member states, which decide independently how and when to open such programs according to national rules and legislation. Doctors who wish to obtain a promising drug for one of their seriously ill patients will need to contact the relevant national authority in their respective country and follow the procedure that has been set up. Typically the national authority keeps a register of the patients treated with the drug within the compassionate use program, and systems are in place to record any side effects reported by the patients or their doctors. Orphan drugs often are subject to compassionate use programs due to their very nature (rare diseases are life-threatening, long-lasting or seriously disabling diseases) and the unusually long time required for both their approval and their effective marketing.

Doctors can also obtain promising drugs for their patients by requesting a supply of a drug from the manufacturer or a pharmacist in another country, to be used for a patient under their direct responsibility. This is often called treatment on a 'named-patient basis' and should not be confused with compassionate use programs. In this case, the doctor responsible for the treatment will either contact the manufacturer directly or make a prescription for a pharmacist. While manufacturers or pharmacists do record what they supply, there is no central register of the group of patients that are being treated in this way.

Reimbursement of Pharmaceutical Products

In the US, many independent third-party payers, as well as the Medicare and state Medicaid programs, reimburse buyers of pharmaceutical products. Medicare is the federal program that provides health care benefits to senior citizens and certain disabled and chronically ill persons. Medicaid is the need-based federal and state program administered by the states to provide health care benefits to certain persons. In return for including our pharmaceutical commercial products in the Medicare and Medicaid formularies, making them eligible for federally funded payments, we will need to agree to pay a rebate to state Medicaid agencies that provide reimbursement for those products. We will also have to agree to sell our commercial products under contracts with the Department of Veterans Affairs, Department of Defense, Public Health Service, and numerous other federal agencies as well as certain hospitals that are designated as 340B covered entities (entities designated by federal statutes to receive

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drugs at discounted prices) at prices that are significantly below the price we charge to commercial pharmaceutical distributors. These programs and contracts are highly regulated and will impose restrictions on our business. Failure to comply with these regulations and restrictions could result in a loss of our ability to continue receiving reimbursement for our drugs once approved. Medicare and Medicaid programs may also seek penalties for improper marketing, including off-label marketing, of our drugs.

Different pricing and reimbursement schemes exist in other countries. In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular drug candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country. There can be no assurance that any country that has price controls or reimbursement limitations for drug products will allow favorable reimbursement and pricing arrangements for any of our products.

Healthcare Law and Regulation/Fraud and Abuse Laws

Healthcare providers, physicians and third-party payers (government or private) often play a primary role in the recommendation and prescription of health care products. In the U.S., numerous detailed requirements apply to government and private health care programs, and a broad range of federal and state fraud and abuse and transparency laws are relevant to pharmaceutical companies. Federal and state healthcare laws and regulations in these areas include the following:

- The federal anti-kickback;
- The federal civil False Claims Act;
- The federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), as amended by the Health Information Technology for Economic and Clinical Health Act (HITECH), and similar state privacy laws;
- The federal criminal false statements statute;
- The federal Physician Payment Sunshine Act, being implemented as the Open Payments Program; and
- Analogous and similar state laws and regulations.

Employees

As of December 31, 2014, we had a total of 89 employees, including 47 in research, clinical, regulatory, medical affairs and quality assurance; 12 in technical operations, manufacturing and quality control; and 30 in general and administrative functions, including pre-commercial activities. We anticipate additional hires in 2015, including country managers in Germany and France who were hired in January 2015.

Our success depends in large measure on our ability to attract and retain capable executive officers and highly skilled employees who are in great demand. None of our employees are represented by a labor union and we believe that our relations with our employees are generally good. Generally,

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our employees are at-will employees. However, we have entered into employment agreements with certain of our executive officers.

Available Information

We file electronically with the Securities and Exchange Commission, or SEC, our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, which we refer to as the Exchange Act. We make available on our website at http://www.insmed.com, free of charge, copies of these reports as soon as reasonably practicable after filing these reports with, or furnishing them to, the SEC. The public can also obtain materials that we file with the SEC through the SEC's website at http://www.sec.gov or at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. Information on the operation of the Public Reference Room is available by calling the SEC at 800-SEC-0330.

Also available through our website's "Investor Relations Corporate Governance" page are charters for the Audit, Compensation and Nominations and Governance committees of our board of directors, our Corporate Governance Guidelines, and our Code of Business Conduct and Ethics.

The references to our website and the SEC's website are intended to be inactive textual references only. Neither the contents of our website, nor the contents of the SEC's website, are incorporated by reference in this Annual Report on Form 10-K.

Financial Information

The financial information required under this Item 1 is incorporated herein by reference to Item 8 of this Annual Report on Form 10-K.

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ITEM 1A. RISK FACTORS

Our business is subject to substantial risks and uncertainties. Any of the risks and uncertainties described below, either alone or taken together, could materially and adversely affect our business, financial condition, results of operations, prospects for growth, or the value of an investment in our common stock. In addition, these risks and uncertainties could cause actual results to differ materially from those expressed or implied by forward-looking statements contained in this Form 10-K (please read the "Cautionary Note Regarding Forward-Looking Statements" appearing at the beginning of this Form 10-K). The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not currently known to us or that we currently deem to be immaterial may also materially and adversely affect our business, financial condition, results of operations, prospects and the value of an investment in our common stock and could cause actual results, performance or achievements to differ materially from those expressed or implied by forward-looking statements.

Risks Related to Development and Commercialization of our Product Candidates

Our near term prospects are highly dependent on the success of our most advanced product candidate, ARIKAYCE. If we are unable to successfully complete the development of, obtain regulatory approval for, and successfully commercialize ARIKAYCE, our business and the value of our common stock may be materially adversely affected.

We are investing substantially all of our efforts and financial resources in the development of ARIKAYCE, our most advanced product candidate. Our ability to generate product revenue from ARIKAYCE, which may not occur for at least the next year or two, if ever, will depend heavily on the successful completion of development of, receipt of regulatory approval for and commercialization of, ARIKAYCE.

Positive results from preclinical studies of a drug candidate may not be predictive of similar results in human clinical trials, and promising results from earlier clinical trials of a drug candidate may not be replicated in later clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in earlier stages of development. Accordingly, the results of the completed clinical trials for ARIKAYCE may not be predictive of the results we may obtain in our clinical trials currently in progress or other trials.

In the fourth quarter of 2014, we filed a MAA with the EMA for ARIKAYCE for the treatment of NTM lung infections as well as *Pseudomonas* lung infections in CF patients. The MAA for ARIKAYCE was validated in February 2015 after the EMA's pediatric committee approved the PIP for ARIKAYCE.

In addition, based on discussions with the FDA, we have commenced with a global phase 3 study which is designed to confirm the positive culture conversion results seen in our phase 2 clinical trial. This confirmatory study is primarily investigating ARIKAYCE for use in non-CF patients with MAC NTM lung infections who have thus far failed their multi-drug treatment regimen.

We do not expect ARIKAYCE or any other drug candidates we may develop to be commercially available for at least the next year or two, if at all.

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We have not completed the research and development stage of ARIKAYCE or any other product candidates other than IPLEX, which we no longer market. If we are unable to successfully commercialize ARIKAYCE or any other products, it may materially adversely affect our business, financial condition, results of operations and our prospects.

Our long-term viability and growth depend on the successful commercialization of ARIKAYCE and potentially other product candidates that lead to revenue and profits. Pharmaceutical product development is an expensive, high risk, lengthy, complicated, resource intensive process. In order to conduct the development programs for our products, we must, among other things, be able to successfully:

- Identify potential drug product candidates;
- Design and conduct appropriate laboratory, preclinical and other research;
- Submit for and receive regulatory approval to perform clinical studies;
- Design and conduct appropriate preclinical and clinical studies according to good laboratory and good clinical practices and disease-specific expectations of FDA and other regulatory bodies;
- Select and recruit clinical investigators;
- Select and recruit subjects for our studies;
- Collect, analyze and correctly interpret the data from our studies;
- Submit for and receive regulatory approvals for marketing;
- Submit for and receive reimbursement approvals for market access: and
- Manufacture the drug product candidates and device components according to cGMP.

The development program with respect to any given product will take many years and thus delay our ability to generate profits. In addition, potential products that appear promising at early stages of development may fail for a number of reasons, including the possibility that the products may require significant additional testing or turn out to be unsafe, ineffective, too difficult or expensive to develop or manufacture, too difficult to administer or unstable. If we do not proceed with the development of our ARIKAYCE program in the NTM or CF indications, certain organizations that provided funding to us for such developmental efforts may elect to proceed with the development of these indications. Even if we are successful in obtaining regulatory approval for our product candidates, including ARIKAYCE, we may not obtain labeling that permits us to market them with commercially viable claims because the final wording of the approved indication may be restrictive, or the available clinical data may not provide adequate comparative data with other products. Failure to successfully commercialize our products will adversely affect our business, financial condition, results of operations and prospects.

If regulatory agencies limit our proposed NTM or CF treatment population for ARIKAYCE, our clinical studies do not produce positive results or our clinical trials are delayed, or if serious side effects are identified during drug development, we may experience delays, incur additional costs and ultimately be unable to commercialize our product candidates in the US, Europe or other countries.

Before obtaining regulatory approval for the sale of our product candidates, we must conduct, at our own expense, extensive preclinical tests to demonstrate the safety of our product candidates in animals, and clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Significant preclinical or clinical trial delays also could shorten the patent protection period during which we may have the exclusive right to commercialize our product candidates. Such delays could allow our competitors to bring products to market before we do and impair our ability to commercialize our products or product candidates.

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Preclinical and clinical testing is expensive, difficult to design and implement and can take many years to complete. Our product development costs have and may continue to increase if we experience further delays in testing or approvals. A failure of one or more of our preclinical studies or clinical trials can occur at any stage of testing. We may experience numerous unforeseen events during, or as a result of, preclinical testing and the clinical trial process that could delay or prevent our ability to obtain regulatory approval or commercialize our product candidates, including:

- Our preclinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials or we may abandon projects that we expect to be promising;
- Regulators or institutional review boards may prevent us from commencing a clinical trial or conducting a clinical trial at a prospective trial site;
- Enrollment in the clinical trials may take longer than expected or the clinical trials as designed may not allow for sufficient patient accrual to complete enrollment of the trial;
- We may decide to limit or abandon our commercial development programs;
- Conditions imposed on us by the FDA or any non-US regulatory authority regarding the scope or design of our clinical trials may require us to collect and submit information to regulatory authorities, ethics committees, institutional review boards or others for review and approval;
- The number of patients required for our clinical trials may be larger than we anticipate or participants may drop out of our clinical trials at a higher rate than we anticipate;
- Our third party contractors, contract research organizations, which we refer to as CROs, clinical investigators, clinical laboratories, product supplier or inhalation device supplier may fail to comply with regulatory requirements or fail to meet their contractual obligations to us in a timely manner;
- We may have to suspend or terminate one or more of our clinical trials if we, the regulators or the institutional review boards determine that the participants are being exposed to unacceptable health risks or for other reasons;
- We may not be able to claim that a product candidate provides an advantage over current standard of care or future competitive therapies in development because our clinical studies may not have been designed to support such claims;
- Regulators or institutional review boards may require that we hold, suspend or terminate clinical research for various reasons, including potential safety concerns or noncompliance with regulatory requirements;
- The cost of our clinical trials may be greater than we anticipate;
- The supply or quality of product used in clinical trials or other materials necessary to conduct our clinical trials may be insufficient or inadequate or we may not be able to reach agreements on acceptable terms with prospective contract manufacturers or CROs; and
- The effects of our product candidates may not be the desired effects or may include undesirable side effects or the product candidates may have other unexpected characteristics.

For example, results from our rodent carcinogenicity study showed that when rats were given ARIKAYCE daily by inhalation for two years, 2 of the 120 rats receiving the highest dose developed lung tumors. These rats received ARIKAYCE doses that were within two-fold of those in clinical studies (normalized on a body surface area basis or a lung weight basis). Based on these results, in 2011 the FDA placed clinical holds on our phase 3 clinical trials for ARIKAYCE, which holds were lifted in 2012. Approvability or labeling of ARIKAYCE may be negatively affected by these results. In 2013, we concluded a 9 month dog inhalation toxicity study. The final report from the study stated that the lung macrophage response in dogs was similar to that seen in our previous 3 month dosing dog study, and there was no evidence of neoplasia, squamous metaplasia or proliferative changes.

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If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete our clinical trials or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- Be delayed in obtaining, or may not be able to obtain, marketing approval for one or more of our product candidates;
- Obtain approval for indications that are not as broad as intended or entirely different than those indications for which we sought approval; or
- Have the product removed from the market after obtaining marketing approval.

We may not have, or may be unable to obtain, sufficient quantities of our product candidates to meet our required supply for clinical studies or commercialization requirements.

We do not have any in-house manufacturing capability other than for development and characterization and depend completely on a small number of third-party manufacturers and suppliers for the manufacture of our product candidates on a clinical or commercial scale. ARIKAYCE and the nebulizer each are supplied by a sole manufacturer. We are dependent on Althea for the production of ARIKAYCE. We do not have a supply agreement with Althea and there is no assurance that we will enter into an agreement or that we will enter into an agreement on terms favorable to us. We are dependent upon PARI for the production and supply of the eFlow Nebulizer System. The inability of a supplier to fulfill our supply requirements could materially adversely affect our ability to obtain and maintain regulatory approvals and future operating results. A change in the relationship with any supplier, or an adverse change in their business, could materially adversely affect our future operating results.

We are dependent upon PARI being able to provide an adequate supply of nebulizers both for our clinical trials and for commercial sale in the event ARIKAYCE receives marketing approval. These nebulizers must be in good working order and meet specific performance characteristics. We intend to work closely with PARI to coordinate efforts regarding regulatory requirements.

We are dependent upon Althea being able to provide an adequate supply of ARIKAYCE both for our clinical trials and for commercial sale in the event ARIKAYCE receives marketing approval. Althea currently manufactures ARIKAYCE at a relatively small scale. In order to meet potential commercial demand if ARIKAYCE is approved, we will need to work with Althea and others, including Therapure, to increase the scale of our manufacturing activities. We intend to work closely with Althea and Therapure to coordinate efforts regarding regulatory requirements and our supply needs.

We do not have long-term commercial agreements with all of our suppliers, including Althea, and if any of our suppliers are unable or unwilling to perform for any reason, we may not be able to locate suppliers or enter into favorable agreements with them. Any inability to acquire sufficient quantities of our components in a timely manner from these third parties could delay clinical trials or commercialization and prevent us from developing and distributing our products in a cost-effective manner or on a timely basis.

In addition, manufacturers of our components are subject to cGMP and similar standards and we do not have control over compliance with these regulations by our manufacturers. If one of our contract manufacturers fails to maintain compliance, the production of our products could be interrupted, resulting in delays and additional costs. In addition, if the facilities of such manufacturers do not pass a pre-approval or post-approval plant inspection, the FDA, as well as other regulatory authorities in jurisdictions outside the US, will not grant approval and may institute restrictions on the

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marketing or sale of our products. We are reliant on third-party manufacturers and suppliers to meet our clinical supply demands and any future commercial products. Delays in receipt of materials, scheduling, release, custom's control and regulatory compliance issues may adversely impact our ability to initiate, maintain or complete clinical trials that we are sponsoring or may adversely impact commercialization. Issues arising from scale-up, facility construction, environmental controls, equipment requirements, local and federal permits and allowances or other factors may have an adverse impact on our ability to manufacture our product candidates.

We have limited experience in conducting and managing the preclinical development activities and clinical trials necessary to obtain regulatory approvals, including approval by the FDA and EMA and other regulatory agencies.

We have limited experience in conducting and managing the preclinical development activities and clinical trials necessary to obtain regulatory approvals, including approval by the FDA and EMA. Since our merger with Transave, we have not completed a regulatory filing and review process for, obtained regulatory approval of or commercialized any of our product candidates. Our limited experience might prevent us from successfully designing, implementing, or completing a clinical trial. The application processes for FDA, EMA and other regulatory agencies are complex and difficult and vary by regulatory agency. We have limited experience in conducting and managing the application processes necessary to obtain regulatory approvals in the various countries and we might not be able to demonstrate that our product candidates meet the appropriate standards for regulatory approval. If we are not successful in conducting and managing our preclinical development activities or clinical trials or obtaining regulatory approvals, we might not be able to commercialize ARIKAYCE, or might be significantly delayed in doing so, which may materially harm our business.

We may not be able to enroll enough patients to complete our clinical trials.

The completion rate of our global phase 3 clinical study of ARIKAYCE for NTM and other future clinical studies of our products is dependent on, among other factors, the patient enrollment rate. Patient enrollment is a function of many factors, including:

- Investigator identification and recruitment;
- Regulatory approvals to initiate study sites;
- Patient population size;
- The nature of the protocol to be used in the trial;
- Patient proximity to clinical sites;
- Eligibility criteria for the study;
- The patients' willingness to participate in the study;
- Competition from other companies' clinical studies for the same patient population; and
- Ability to obtain any necessary comparator drug or medical device.

We believe our procedures for enrolling patients to date have been appropriate. However, delays in patient enrollment for future clinical trials could increase costs and delay ultimate commercialization and sales, if any, of our products.

If any of our products meet the criteria for approval pursuant to Subpart H (accelerated approval), such approval will be subject to our carrying out, with due diligence, adequate and well-controlled post market studies to verify and describe their clinical benefit. If we fail to complete such studies with due diligence, or if the results of such studies fail to demonstrate clinical benefit, FDA may, following a hearing, withdraw product approval.

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The commercial success of ARIKAYCE or any other product candidates that we may develop will depend upon many factors, including the degree of market acceptance by physicians, patients, third-party payers and others in the medical community.

Even if we are able to successfully complete development of, obtain regulatory approval for, and bring ARIKAYCE to market, ARIKAYCE may not gain market acceptance by physicians, patients, third-party payers and others in the medical community. If ARIKAYCE, or any other products we bring to market, do not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not become profitable. The degree of market acceptance of ARIKAYCE and any other product candidates, if approved for commercial sale, will depend on a number of factors, including:

- The prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- The efficacy and potential advantages over alternative treatments;
- The pricing of our product candidates;
- Relative convenience and ease of administration;
- The willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- The strength of marketing and distribution support and timing of market introduction of competitive products;
- Publicity concerning our products or competing products and treatments, including competing products becoming subject to generic pricing; and
- Sufficient third party insurance coverage or reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical and clinical trials, market acceptance of the product will not be known until after it is launched. For example, if a clinical trial is not designed to demonstrate advantages over alternative treatments, we may be prohibited from promoting our product candidates on any such advantages. Our efforts to educate the medical community and third-party payers on the benefits of our product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by more established technologies marketed by our competitors.

We currently have a very small marketing or sales organization, and we have limited experience as a company in marketing drug products. If we are unable to establish our own marketing and sales capabilities, or are unable to enter into agreements with third parties, to market and sell our products after they are approved, we may not be able to generate product revenues.

We have a very small commercial organization for the marketing, market access, sales and distribution of any drug products. In order to commercialize ARIKAYCE or any other product candidates, we must develop these capabilities on our own or make arrangements with third parties for the marketing, sales and distribution of our products. The establishment and development of our own sales force would be expensive and time consuming and could delay any product launch, and we cannot be certain that we would be able to successfully develop this capability. As a result, we may seek one or more partners to handle some or all of the sales and marketing of ARIKAYCE. However, we may not be able to enter into arrangements with third parties to sell ARIKAYCE on favorable terms or at all. In the event we are unable to develop our own marketing, market access, and sales force or collaborate with a third-party marketing, market access, and sales organization, we may not be able to successfully commercialize ARIKAYCE or any other product candidates that we develop, which would adversely affect our ability to generate product revenues. Further, whether we commercialize products on our

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own or rely on a third party to do so, our ability to generate revenue will be dependent on the effectiveness of the sales force.

Promotional materials for our approved drug products must be submitted, along with Form 2253, to FDA's Office of Prescription Drug Products (OPDP) at the time of initial dissemination or publication. For products approved pursuant to Subpart H, promotional materials intended to be used during product launch must be submitted during the pre-approval review period, at least 30 days prior to the intended time of initial dissemination or publication. For other products, OPDP encourages pre-launch review, and will provide advisory comments in response to such submissions upon request. There is no guarantee that OPDP will agree that the proposed promotional materials comply with applicable FDA requirements. A negative response in OPDP Advisory Comments may require us to revise planned promotional materials and may limit the claims we can use in such materials. If OPDP considers promotional materials already disseminated or published to violate applicable FDA requirements, OPDP may initiate enforcement action, including Untitled Letters/Notices of Violation, Warning Letters, Injunction/Consent decree, Seizures/Criminal action, and/or Civil and monetary penalties.

We have limited experience operating internationally, are subject to a number of risks associated with our international activities and operations and may not be successful in our efforts to expand internationally.

We have manufacturing, collaboration, clinical trial and other relationships outside the United Sates but we currently have very limited operations outside of the United States. In order to meet our long-term goals, we will need to grow our international operations over the next several years. Consequently, we are and will continue to be subject to additional risks related to operating in foreign countries, including:

- the fact that we have limited experience operating our business internationally;
- we may not achieve the optimal pricing and reimbursement for ARIKAYCE;
- there may be fewer addressable NTM and/or CF patients than were originally forecasted;
- unexpected adverse events related to ARIKAYCE or our other product candidates that occur in foreign markets that we have not experienced in the United States;
- local, economic and political conditions, including geopolitical events, such as war and terrorism, foreign currency fluctuations, which could result in increased or unpredictable operating expenses and reduced revenues and other obligations incident to doing business in, or with a company located in, another country;
- unexpected changes in reimbursement and pricing requirements, tariffs, trade barriers and regulatory requirements;
- economic weakness, including foreign currency exchange risks, inflation or political instability in particular foreign economies and markets; and
- compliance with foreign or U.S. laws, rules and regulations, including data privacy requirements, labor relations laws, tax laws, anti- competition regulations, import, export and trade restrictions, anti-bribery/anti-corruption laws, regulations or rules, which could lead to actions by us or our licensees, distributors, manufacturers, other third parties who act on our behalf or with whom we do business in foreign countries or our employees who are working abroad that could subject us to investigation or prosecution under such foreign or U.S. laws.

These and other risks associated with our international operations may materially adversely affect our business and results of operations.

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Risks Related to Our Reliance on Third Parties

We rely on third parties including clinical research organizations, or CROs, clinical laboratories, analytical laboratories and other providers for many services. If we are unable to form and sustain these relationships, or if any third-party arrangements that we may enter into are unsuccessful, our ability to develop and commercialize our products may be materially adversely affected.

We currently rely, and expect that we will in the future continue to rely, on third parties for significant research, analytical services, preclinical development and clinical development. For example, almost all of our clinical trial work is done by CROs and clinical laboratories. Reliance on these third parties poses a number of risks, including the following:

- We may face significant competition in seeking appropriate partners;
- These arrangements are complex and time consuming to negotiate, document and implement;
- We may not be successful in our efforts to establish and implement collaborations or other alternative arrangements that we might pursue on favorable terms;
- We may not be able to effectively control whether the CROs or other third parties will devote sufficient resources to our programs or products;
- We are not able to control the regulatory compliance of CROs, third-party suppliers, contractors and collaborators, including their processes and procedures, systems utilized to collect and analyze data, and equipment used to test drug product and/or clinical supplies;
- Disagreements with third parties and CROs may be difficult to resolve and could result in a dispute over and loss of intellectual property rights, delay or termination of the research, development, or commercialization of product candidates or result in litigation or arbitration;
- Contracts with our collaborators may fail to provide sufficient protection of our intellectual property; and
- We may have difficulty enforcing the contracts if one of these collaborators fails to perform.

A great deal of uncertainty exists regarding the success of any current and future third-party efforts on which we might depend. Failure of these efforts could delay, impair, or prevent the development and commercialization of our products and adversely affect our business, financial condition, results of operations and prospects.

We rely on PARI, a third party manufacturer, to supply the nebulizer that is exclusively used for ARIKAYCE. Any disruption in supply of the nebulizer will have a material adverse effect on our business.

We are dependent upon PARI being able to provide an adequate supply of nebulizers both for our clinical trials and for commercial sale in the event ARIKAYCE receives marketing approval. These nebulizers must be in good working order, meet specific performance characteristics and be approved by FDA and other regulatory agencies along with ARIKAYCE. We have no alternative supplier for the nebulizer and we do not intend to seek an alternative or secondary supplier of nebulizers. Significant effort and time were expended in the optimization of the nebulizer for use with ARIKAYCE. In the event PARI cannot provide devices replication of the optimized device by another party may require considerable time and additional regulatory approval. PARI has the right to terminate this agreement upon written notice for our uncured material breach, if we are the subject of specified bankruptcy or liquidation events, if we assign or otherwise transfer the agreement to a third party that does not agree to assume all of our rights and obligations set forth in the agreement, or if we fail to reach certain specified milestones, including the requirement that we use commercially reasonable efforts to develop, commercialize, market, and sell ARIKAYCE for use in CF indications in one or more countries (and at least in the US). In the event PARI terminates the supply agreement and ceases to manufacture the nebulizer, we cannot be certain that we would be able identify another willing supplier for the nebulizer

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on terms we require. A disruption in the supply of nebulizers could delay, impair, or prevent the development and commercialization of our products and adversely affect our business, financial condition, results of operations and prospects.

We rely on Althea, a third party manufacturer, to supply ARIKAYCE. Any disruption in the supply of ARIKAYCE could have a material adverse effect on our business.

We are dependent upon Althea being able to provide an adequate supply of ARIKAYCE both for our clinical trials and for commercial sale in the event ARIKAYCE receives marketing approval. We do not have a supply agreement with Althea and are currently purchasing under a purchase order basis. There can be no assurance that we will enter into a supply agreement or that we will enter into an agreement on terms favorable to us. In 2013, Althea was acquired by Ajinomoto Co., a global manufacturing company based in Japan and now operates as Ajinomoto Althea, Inc.

Althea currently manufactures ARIKAYCE at a relatively small scale. In order to meet potential commercial demand, if ARIKAYCE is approved, we have identified Therapure in Canada as an alternate site of manufacture that operates at a larger scale. Therapure may not be able to successfully transfer the ARIKAYCE manufacturing process to their site, or we may not be able to obtain regulatory approvals for ARIKAYCE produced at Therapure's facility. We may not be able to secure an alternative source of ARIKAYCE at an adequate scale of production.

We currently depend on third parties to conduct the operations of our clinical trials.

We rely on third parties, such as CROs, medical institutions, clinical investigators and contract laboratories to oversee some of the operations of our clinical trials and to perform data collection and analysis. As a result, we may face additional delays outside of our control if these parties do not perform their obligations in a timely fashion or in accordance with regulatory requirements. If these third parties do not successfully carry out their contractual duties or obligations and meet expected deadlines, if they need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or for other reasons, our financial results and the commercial prospects for ARIKAYCE or our other potential product candidates could be materially harmed, our costs could increase and our ability to obtain regulatory approval and commence product sales could be delayed.

We also rely on third parties to select and enter into agreements with clinical investigators to conduct clinical trials to support approval of our products and the failure of these third parties to carry out such evaluation and selection can adversely affect the quality of the data from these studies and, potentially, the approval of our products. In particular, as part of our new drug approval submissions, we must disclose any financial interests of investigators who participated in any of the clinical studies being submitted in support of approval, or must certify to the absence of such financial interests. FDA evaluates the information contained in such disclosures to determine whether disclosed interests may have an impact on the reliability of a study. If FDA determines that financial interests of any clinical investigator raise serious questions of data integrity, FDA can institute a data audit, request that we submit further data analyses, conduct additional independent studies to confirm the results of the questioned study, or refuse to use the data from the questioned study as a basis for approval. A finding by FDA, that a financial relationship of an investigator raise serious questions of data integrity, could delay or otherwise adversely affect approval of our products.

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Risks Related to Our Financial Condition and Capital Requirements

We have a history of operating losses. We expect to incur operating losses for the foreseeable future and may never achieve or maintain profitability.

We are a biopharmaceutical company focused on developing and commercializing inhaled therapies for patients battling serious lung diseases that are often life threatening. We have incurred losses each previous year of our operation, except in 2009, when we sold our manufacturing facility and certain other assets to Merck. We expect to continue incurring operating losses for the foreseeable future. The process of developing and commercializing our products requires significant pre-clinical and clinical testing as well as regulatory approvals for commercialization and marketing before we are allowed to begin product sales. In addition, commercialization of our drug candidates likely would require us to establish a sales and marketing organization and contractual relationships to enable product manufacturing and other related activities. We expect that our activities, together with our general and administrative expenses, will continue to result in substantial operating losses for the foreseeable future. As of December 31, 2014, our accumulated deficit was $470.8 million. For the year ended December 31, 2014, our consolidated net loss was $79.2 million.

To achieve and maintain profitability, we need to generate significant revenues from future product sales. This will require us to be successful in a range of challenging activities, including:

- Successfully completing development of and obtaining regulatory approval for the marketing of ARIKAYCE and possibly other product candidates which have yet to be developed and which would also require marketing approval;
- Commercializing ARIKAYCE and any other product candidates for which we obtain marketing approval; and
- Achieving market acceptance and reimbursement of ARIKAYCE and any other product candidates for which we obtain marketing approval in the medical community and with patients and third-party payers.

ARIKAYCE will require marketing approval and significant investment in commercial capabilities, including manufacturing and sales and marketing efforts, before its product sales can generate any revenues for us. Because of the numerous risks and uncertainties associated with drug development and commercialization, we are unable to predict the extent of any future losses. We may never successfully commercialize ARIKAYCE or any other products, generate significant future revenues or achieve and sustain profitability.

We expect that we will need additional funds in the future to continue our operations, but we face uncertainties with respect to our ability to access capital.

Our operations have consumed substantial amounts of cash since our inception. We expect to continue to incur substantial research and development expenses, and we expect to expend substantial financial resources to complete development of, seek regulatory approval for, and prepare for commercialization of ARIKAYCE. We may need to seek additional funding in order to complete any clinical trials related to ARIKAYCE, seek regulatory approvals of ARIKAYCE, and commercially launch ARIKAYCE. We also may require additional future capital in order to continue our other research and development activities or to acquire complementary technology. As of December 31, 2014, we had $159.2 million of cash and cash equivalents on hand. If adequate funds are not available to us when needed, we may be required to reduce or eliminate research and development programs or commercial efforts.

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Our future capital requirements will depend on many factors, including factors associated with:

- Phase 2 and phase 3 clinical trials and commercialization of ARIKAYCE;
- Early access programs;
- Non-clinical and clinical testing;
- Process development and scale up for manufacturing;
- Manufacturing;
- Performance of our third-party suppliers and manufacturers;
- Obtaining marketing, sales and distribution capabilities;
- Obtaining regulatory approvals;
- Research and development, including formulation development;
- Retaining employees and consultants;
- Global expansion efforts;
- Filing and prosecuting patent applications and enforcing and defending patent claims;
- Establishing strategic alliances and collaborations with third-parties; and
- Current and potential future litigation.

We also may need to spend more funds than currently expected because we may further change or alter drug development plans, acquire additional drugs or drug candidates or we may misjudge our costs. As of December 31, 2014, we had no committed sources of capital and do not know whether additional financing will be available when needed, or, if available, that the terms will be favorable. We cannot assure that our cash reserves together with any subsequent funding will be sufficient for our capital requirements. The failure to satisfy our capital requirements will adversely affect our business, financial condition, results of operations and prospects.

We may seek additional funding through strategic alliances, private or public sales of our securities, debt financing or licensing all or a portion of our technology or through other means. Such funding may significantly dilute existing shareholders, subject us to contractual restrictions such as operating or financial covenants or limit our rights to our technology.

We currently have no meaningful source of revenue.

In 2014 and 2012, we generated no revenue. In 2013, we generated other revenue from the modification of a previously granted license of our IPLEX technology. Unless we can execute one or more revenue generating transactions or successfully obtain regulatory approval for and commercialize ARIKAYCE, we will have no material sources of operating revenue. We expect to continue to incur substantial additional operating losses for at least the next several years as we continue to develop and seek to commercialize ARIKAYCE.

If we are not successful in our efforts to evaluate potential future IPLEX initiatives and to identify and engage in possible out- licensing opportunities for IPLEX, we may not derive any future revenues from IPLEX.

IPLEX is no longer a development priority for us. We no longer have protein development capability or the in-house capability to manufacture IPLEX. Accordingly, we continue to evaluate possible out-licensing opportunities for IPLEX. We may have difficulty identifying possible markets and prospective partners for out-licensing. Even if we are able to enter into out-licensing arrangements, we may not derive any revenue from those arrangements.

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Our loan agreement with Hercules Technology Growth Capital, Inc. ("Hercules") contains covenants that impose restrictions on our operations that may adversely affect our ability to optimally operate our business or to maximize shareholder value.

Our loan agreement with Hercules contains various restrictive covenants, including restrictions on our ability to incur additional debt, transfer or place a lien or security interest on our assets, including our intellectual property, merge with or acquire other companies, redeem or repurchase any shares of our capital stock or pay cash dividends to our stockholders. The loan agreement also contains certain other covenants (including limitations on other indebtedness, liens, acquisitions, investments and dividends), and events of default (including payment defaults, breaches of covenants following any applicable cure period, a material impairment in the perfection or priority of the lender's security interest or in the collateral, and events relating to bankruptcy or insolvency). Upon the occurrence of an event of default, a default interest rate of an additional 5% may be applied to the outstanding loan balances, and the lender may terminate its lending commitment, declare all outstanding obligations immediately due and payable, and take such other actions as set forth in the Loan Agreement. In addition, pursuant to the Loan Agreement, the lender has the right to participate, in an amount of up to $1.0 million, in certain future private equity financing(s). Our borrowings under the Loan Agreement are secured by a lien on our assets, excluding our intellectual property, and in the event of a default on the loan, the lender may have the right to seize our assets securing our obligations under the Loan Agreement. The terms and restrictions provided for in the Loan Agreement may inhibit our ability to conduct our business and to provide distributions to our stockholders. Future debt securities or other financing arrangements could contain negative covenants similar to, or even more restrictive than, the Hercules loan.

In process research and development (IPRD) currently comprises approximately 25% of our total assets. A reduction in the value of our IPRD could impact our results of operations and financial condition.

As a result of the merger with Transave we recorded an intangible IPRD asset of $77.9 million and goodwill of $6.9 million on our balance sheet. As a result of our clinical hold announced in late 2011 we recorded a charge of $26.0 million in the fourth quarter of 2011 and reduced the value of IPRD to $58.2 million and reduced goodwill to zero. Other potential future activities or results could result in additional write-downs of IPRD, which would adversely affect our results of operations.

We may be unable to use our net operating losses.

We have substantial tax loss carry forwards for US federal income tax purposes. Our ability to fully use certain carry forwards prior to December 2010 to offset future income or tax liability was limited under section 382 of the Internal Revenue Code of 1986, as amended. Changes in the ownership of our stock, including those resulting from the issuance of shares of our common stock upon exercise of outstanding warrants or options, may limit or eliminate our ability to use certain net operating losses in the future.

Risks Related to Regulatory Matters

We may not be able to obtain regulatory approvals for ARIKAYCE or any other products we develop in the US, Europe or other countries. If we fail to obtain such approvals, we will not be able to commercialize our products.

We are required to obtain various regulatory approvals prior to studying our products in humans and then again before we market and distribute our products. The regulatory review and approval processes in both the US and Europe require evaluation of preclinical studies and clinical

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studies, as well as the evaluation of our manufacturing process. These processes are complex, lengthy, expensive, resource intensive and uncertain. Securing regulatory approval to market our products requires the submission of much more extensive preclinical and clinical data, manufacturing information regarding the process and facility, scientific data characterizing our product and other supporting data to the regulatory authorities in order to establish its safety and effectiveness. This process also is complex, lengthy, expensive, resource intensive and uncertain. We have limited experience in submitting and pursuing applications necessary to gain these regulatory approvals.

Data submitted to the regulators is subject to varying interpretations that could delay, limit or prevent regulatory agency approval. We may also encounter delays or rejections based on changes in regulatory agency policies during the period in which we develop a product and the period required for review of any application for regulatory agency approval of a particular product.

Delays in obtaining regulatory agency approvals could adversely affect the development and marketing of any drugs that we or any third parties develop. Resolving such delays could force us or third parties to incur significant costs, could limit our allowed activities or the allowed activities of third parties, could diminish any competitive advantages that we or our third parties may attain or could adversely affect our ability to receive royalties, any of which could materially adversely affect our business, financial condition, results of operations or prospects.

To market our products outside of the US and, Europe, we and any potential third parties must comply with numerous and varying regulatory requirements of other countries. The approval procedures vary among countries and can involve additional product testing and administrative review periods. The time required to obtain approval in these other territories might differ from that required to obtain FDA or EMA approval. The regulatory approval process in these other territories includes at least all of the risks associated with obtaining FDA and EMA approval detailed above.

Specifically related to INS1009, we believe that this product could be eligible for approval under Section 505(b)(2) of the FDCA. Like a traditional NDA that is submitted under Section 505(b)(1) of the FDCA, a 505(b)(2) NDA must include full safety and effectiveness reports, but unlike a traditional NDA the applicant may rely at least in part on studies not conducted by or for the applicant. The ability to rely on existing data to support safety and/or effectiveness can reduce the time and cost associated with traditional NDAs. We cannot be sure that we will obtain approval for INS1009 under the 505(b)(2) pathway.

Approval by the FDA or the EMA does not ensure approval by the regulatory authorities of other countries. Marketing approval in one country does not ensure marketing approval in another, but a failure or delay in obtaining marketing approval in one country may have a negative effect on the regulatory process in others. In addition, we may be subject to fines, suspension or withdrawal of marketing approvals, product recalls, seizure of products, operating restrictions and criminal prosecution if we fail to comply with applicable US and foreign regulatory requirements. If we fail to comply with regulatory requirements or to obtain and maintain required approvals, our target market may be reduced and our ability to realize the full market potential of our product candidates may be harmed. The failure to obtain such approvals may materially adversely affect our business, financial condition, results of operations and our prospects.

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There is little or no precedent for clinical development and regulatory expectations for agents to treat NTM; as a result we may encounter challenges developing clinical endpoints that will ultimately be satisfactory to regulators, and may need to reevaluate our surrogate endpoints at various points in time.

FDA may base accelerated approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint (other than survival or irreversible morbidity). FDA regulations referred to as "Subpart H Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" describe the potential use of surrogate endpoints. A surrogate endpoint used for accelerated approval is a marker a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality. The FDA bases its decision on whether to accept the proposed surrogate or intermediate clinical endpoint on the scientific support for that endpoint. Studies that demonstrate a drug's effect on a surrogate or intermediate clinical endpoint must be "adequate and well controlled" as required by the FD&C Act.

If a drug is approved based on a surrogate endpoint under Subpart H the approval will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Post marketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

For ARIKAYCE to be successfully developed and commercialized, in addition to regulatory approvals required for ARIKAYCE, the eFlow nebulizer system must satisfy certain regulatory requirements and its use as a delivery system for ARIKAYCE must be approved for use in any market in which we intend to commercialize ARIKAYCE.

Although the optimized eFlow Nebulizer System is CE marked by PARI in Europe, outside Europe it is labeled as investigational for use in our clinical trials in the US, Canada, Australia and Japan. The optimized eFlow Nebulizer System is not approved for commercial use in the US, Canada or certain other markets in which we may choose to commercialize ARIKAYCE if approved. The eFlow Nebulizer System must receive regulatory approval before we can market ARIKAYCE. We will continue to work closely with PARI to coordinate efforts regarding regulatory requirements, including our proposed filings for a drug and device.

Even if we obtain marketing approval for ARIKAYCE or any of our other product candidates, we will continue to face extensive regulatory requirements and our products may face future development and regulatory difficulties.

Even if marketing approval in the US is obtained, the FDA may still impose significant restrictions on a product's indicated uses or marketing, including risk evaluation and mitigation strategies, or may impose ongoing requirements on us, including with respect to:

- Labeling, such as black box or other warnings or contraindications;
- Post-market surveillance, post-market studies or post-market clinical trials;
- Packaging, storage, distribution, safety surveillance, advertising, promotion, recordkeeping and reporting of safety and other post-market information;
- Monitoring and reporting adverse events and instances of the failure of a product to meet the specifications in the NDA;

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- Changes to the approved product, product labeling or manufacturing process;
- Advertising and other promotional material; and
- Disclosure of clinical trial results on publicly available databases.

In addition, the third-party manufacturers of our products and their facilities are and will be subject to continual review and periodic inspections by the FDA and other regulatory authorities. The distribution, sale and marketing of our products are subject to a number of additional requirements, including:

- State wholesale drug distribution laws and the distribution of our product samples to physicians must comply with the requirements of the Prescription Drug Marketing Act;
- Sales, marketing and scientific or educational grant programs must comply with the anti-kickback and fraud and abuse provisions of the Social Security Act, the transparency provision of the Patient Protection and Affordable Care Act and an associated reconciliation bill that became law in March 2010, which we refer to collectively as the Health Care Reform Law, federal and state patient privacy laws, the False Claims Act and similar state laws; and
- Pricing and rebate programs must comply with the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990 and the Veteran's Health Care Act of 1992, and if products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply.

All of these activities also may be subject to federal and state consumer protection and unfair competition laws.

We also are subject to changes or revisions to these laws and regulations that may make gaining regulatory approval, reimbursement and pricing more difficult or at least subject to different criteria and standards.

If we or any third party involved in our manufacturing or commercialization efforts fail to comply with applicable regulatory requirements, a regulatory agency may:

- Issue warning letters or untitled letters asserting that we are in violation of the law;
- Seek an injunction or impose civil or criminal penalties or monetary fines;
- Suspend or withdraw marketing approval;
- Suspend any ongoing clinical trials;
- Refuse to approve pending applications or supplements to applications submitted by us;
- Suspend or impose restrictions on operations, including costly new manufacturing requirements;
- Seize or detain products, refuse to permit the import or export of products, or require us to initiate a product recall;
- Refuse to allow us to enter into supply contracts, including government contracts;
- Impose civil monetary penalties; or
- Pursue civil or criminal prosecutions and fines against our company or responsible officers.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenues.

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Even if we obtain marketing approval for ARIKAYCE or any of our other product candidates, adverse effects discovered after approval could limit the commercial profile of any approved product.

If we obtain marketing approval for ARIKAYCE or any other product candidate that we develop, such products will be used by a larger number of patients and for longer periods of time than they were used in clinical trials. For these reasons or other reasons, we or others may later discover that our products have adverse effect profiles that limit their usefulness or require their withdrawal. This discovery could have a number of potentially significant negative consequences, including:

- Regulatory authorities may withdraw their approval of the product;
- Regulatory authorities may require the addition of labeling statements, such as black box or other warnings or contraindications;
- Regulatory authorities may require us to issue specific communications to healthcare professionals, such as "Dear Doctor Letters;"
- Regulatory authorities may impose additional restrictions on marketing and distribution of the products;
- Regulatory authorities may issue negative publicity regarding the product, including safety communications;
- We may be required to change the way the product is administered, conduct additional clinical studies or restrict the distribution of the product;
- We could be sued and held liable for harm caused to subjects;
- We could be subject to negative publicity; and
- Our reputation may suffer.

Any of these events could prevent us from maintaining market acceptance of the affected product, could cause substantial reduction of sales, could substantially increase the costs of commercializing our product candidates, and could cause significant financial losses.

If we are unable to obtain adequate reimbursement from governments or third-party payers for ARIKAYCE or any other products that we may develop or if we are unable to obtain acceptable prices for those products, our prospects for generating revenue and achieving profitability may be materially adversely affected.

Our prospects for generating revenue and achieving profitability depend heavily upon the availability of adequate reimbursement for the use of our approved product candidates from governmental and other third-party payers, both in the US and in other markets. Reimbursement by a third party payer may depend upon a number of factors, including the third party payer's determination that use of a product is:

- A covered benefit under its health plan;
- Safe, effective and medically necessary;
- Appropriate for the specific patient;
- Cost-effective; and
- Neither experimental nor investigational.

Obtaining reimbursement approval for a product from each government or other third-party payer is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost effectiveness data for the use of our products to each payer. We may not be able to provide data sufficient to gain acceptance with respect to reimbursement or we might need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to such payers' satisfaction. Such studies might require us to commit a significant amount of management time and financial and other resources. Even when a payer determines that a product is eligible for

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reimbursement, the payer may impose coverage limitations that preclude payment for some uses that are approved by the FDA or non-US regulatory authorities. In addition, there is a risk that full reimbursement may not be available for high priced products. Moreover, eligibility for coverage does not imply that any product will be reimbursed in all cases or at a rate that allows us to make a profit or even cover our costs. Interim payments for new products, if applicable, also may not be sufficient to cover our costs and may not be made permanent. Subsequent approvals of competitive products could result in a detrimental change to the reimbursement of our products.

There is a significant focus in the US healthcare industry and elsewhere on cost containment and value. We expect changes in the Medicare program and state Medicaid programs, as well as managed care organizations and other third-party payers to continue to put pressure on pharmaceutical product pricing in return for near-term cost effectiveness or budget impact. In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for drugs. In addition, this legislation authorized Medicare Part D prescription drug plans to use formularies where they can limit the number of drugs that will be covered in any therapeutic class. As a result of this legislation and the expansion of federal coverage of drug products, we expect that there will be additional pressure to contain and reduce costs. These cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products and could seriously harm our business. Although the MMA applies only to drug benefits for Medicare beneficiaries, private payers often follow Medicare coverage policy and payment limitations when setting their own reimbursement rates, and any reimbursement reduction resulting from the MMA may result in a similar reduction in payments from private payers.

In March 2010, the Patient Protection and Affordable Care Act, or PPACA, which was intended to broaden access to health insurance, constrain and reduce the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms, was passed into law. Effective in October 2010, the PPACA revised the definition of "average manufacturer price" for reporting purposes, which could increase the amount of Medicaid drug rebates to states. Further, beginning in 2011, the new law imposed a significant annual fee on companies that manufacture or import branded prescription drug products. We do not know the full effects that the PPACA will have on our commercialization efforts but we believe it is likely that the law will continue the pressure on pharmaceutical pricing, especially under the Medicare program, and also may increase our regulatory burdens and operating costs. If one or more of our product candidates reaches commercialization, such changes may have a significant impact on our ability to set a price we believe is fair for our products and may adversely affect our ability to generate revenue and achieve or maintain profitability. We expect further federal and state proposals and health care reforms to continue to be proposed by legislators, which could limit the prices that can be charged for the products we develop and may limit our commercial opportunity.

Moreover, in markets outside the US, including Japan, Canada and the countries in the EU, pricing of pharmaceutical products is subject to governmental control. Evaluation criteria used by many EU government agencies for the purposes of pricing and reimbursement typically focus on a product's degree of innovation and its ability to meet a clinical need unfulfilled by currently available therapies. The PPACA created a similar entity, the Patient-Centered Outcomes Research Institute (PCORI) designed to review the effectiveness of treatments and medications in federally-funded health care programs. The PCORI began its first research initiatives recently, and an adverse result may result in a treatment or product being removed from Medicare or Medicare coverage. The decisions of such governmental agencies could affect our ability to sell our products profitably.

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Government health care reform could increase our costs, and could adversely affect our revenue and results of operations.

Our industry is highly regulated and changes in law may adversely impact our business, operations or financial results. Substantial new requirements affecting compliance were enacted as part of PPACA, which may require us to modify our business practices with health care practitioners. For example, drug manufacturers are required to report information on payments or transfers of value to U.S. physicians and teaching hospitals as well as investment interests held by physicians and their immediate family members during the preceding calendar year. Failure to submit required information may result in civil monetary penalties. The reported data began to be posted in searchable form on a public website on September 30, 2014. In addition, other countries, including France, require the disclosure of certain payments to health care professionals.

The reforms imposed by the new law will significantly impact the pharmaceutical industry; however, the full effects cannot be known until these provisions are implemented and CMS and other federal and state agencies issue applicable regulations or guidance. Moreover, in the coming years, additional changes could be made to governmental healthcare programs that could significantly impact the success of our products or product candidates. We will continue to evaluate the PPACA, as amended, the implementation of regulations or guidance related to various provisions of the PPACA by federal agencies, as well as trends and changes that may be encouraged by the legislation and that may potentially have an impact on our business over time. The cost of implementing more detailed record keeping systems and otherwise complying with these requirements could substantially increase our costs.

We will need approval from the FDA and other regulatory authorities in jurisdictions outside the US for our proposed trade names. Any failure or delay associated with such approvals may delay the commercialization of our products.

Any trade name we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the US Patent and Trademark Office, or PTO. The FDA typically conducts a rigorous review of proposed trade names, including an evaluation of potential for confusion with other trade names and medication error. The FDA also may object to a trade name if it believes the name is inappropriately promotional. The FDA approved our use of the name ARIKAYCE as our proposed trade name for our liposomal amikacin for inhalation product candidate. Even after the FDA approves a trade name, the FDA may request that we adopt an alternative name for the product if adverse event reports indicate a potential for confusion with other trade names and medication error. If we are required to adopt an alternative name, the commercialization of ARIKAYCE could be delayed or interrupted, which would limit our ability to commercialize ARIKAYCE and generate revenues. In December 2012, we learned that the EMA had no objection to our request to use the names ARIKACE or ARIKAYCE.

Our growth depends on technologies that may not be available on terms acceptable to us or at all.

As part of our business strategy, we may in-license new products and technologies. Nonetheless, we cannot assure you that we will identify suitable products or enter into such license agreements on acceptable terms. Upfront cash payments for in-licensed products and technologies will decrease our cash balances and may accelerate the need to raise additional capital.

We may enter into collaborative relationships that would involve our collaborators conducting proprietary development programs. Any conflict with our collaborators could limit our ability to obtain future collaboration agreements and negatively influence our relationship with existing collaborators. Disagreements with collaborators may also develop over the rights to our intellectual property.

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Certain of our collaborators could be or become competitors of ours. Our collaborators could harm our product development and commercialization efforts by:

- Developing competing products;
- Precluding us from entering into collaborations with their competitors;
- Failing to obtain regulatory approvals;
- Terminating their agreements with us prematurely; or
- Failing to devote sufficient resources to the development and commercialization of products.

If we are found in violation of federal or state "fraud and abuse" laws, we may be required to pay a penalty or may be suspended from participation in federal or state health care programs, which may adversely affect our business, financial condition and results of operations.

In the United States, we are subject to various federal and state health care "fraud and abuse" laws, including anti-kickback laws, false claims laws and other laws intended to reduce fraud and abuse in federal and state health care programs. The federal Anti-Kickback Statute makes it illegal for any person, including a prescription drug manufacturer or a party acting on its behalf, to knowingly and willfully solicit, receive, offer or pay any remuneration that is intended to induce the referral of business, including the purchase, order or prescription of a particular drug for which payment may be made under a federal health care program, such as Medicare or Medicaid. Under federal government regulations, some arrangements, known as safe harbors, are deemed not to violate the federal Anti-Kickback Statute. Although we seek to structure our business arrangements in compliance with all applicable requirements, these laws are broadly written, and it is often difficult to determine precisely how the law will be applied in specific circumstances. Accordingly, it is possible that our practices may be challenged under the federal Anti-Kickback Statute. False claims laws prohibit anyone from knowingly and willfully presenting or causing to be presented for payment to third-party payers, including government payers, claims for reimbursed drugs or services that are false or fraudulent, claims for items or services that were not provided as claimed, or claims for medically unnecessary items or services. Cases have been brought under false claims laws alleging that off-label promotion of pharmaceutical products or the provision of kickbacks has caused health care providers to submit false claims to governmental health care programs when they prescribe drugs or fill prescriptions for off-label purposes. Under the Health Insurance Portability and Accountability Act of 1996, we are prohibited from knowingly and willfully executing a scheme to defraud any health care benefit program, including private payers, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for health care benefits, items or services. Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including fines or exclusion or suspension from federal and state health care programs such as Medicare and Medicaid and debarment from contracting with the U.S. government. In addition, private individuals have the ability to bring actions on behalf of the government under the federal False Claims Act as well as under the false claims laws of several states.

Many states have adopted laws similar to the federal anti-kickback statute, some of which apply to the referral of patients for health care services reimbursed by any source, not just governmental payers. In addition, California and a few other states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America, or PhRMA, Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. Health record privacy laws may limit access to information identifying those individuals who may be prospective users or prohibit contact with any persons enrolled in Medicare or Medicaid. There are ambiguities as to what is required to comply with these state requirements, and we could be subject

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to penalties if a state determines that we have failed to comply with an applicable state law requirement.

Neither the government nor the courts have provided definitive guidance on the application of fraud and abuse laws to our business. Law enforcement authorities are increasingly focused on enforcing these laws, and it is possible that some of our practices may be challenged under these laws. While we believe we have structured our business arrangements to comply with these laws, it is possible that the government could allege violations of, or convict us of violating, these laws. If we are found in violation of one of these laws, we could be required to pay a penalty and could be suspended or excluded from participation in federal or state health care programs, and our business, financial condition and results of operations may be adversely affected.

Risks Related to Our Intellectual Property

If we are unable to protect our intellectual property rights adequately, the value of our product candidates could be diminished.

Our success will depend in part on our ability to protect proprietary technology and to obtain patent protection for our products, prevent third parties from infringing on our patents and refrain from infringing on the patents of others, both domestically and internationally.

In addition, the patent situation in the field of biotechnology and pharmaceuticals generally is highly uncertain and involves complex legal, technical, scientific and factual questions. We intend to actively pursue patent protection for products resulting from our research and development activities that have significant potential commercial value. We may not be able to obtain additional issued patents relating to our technology or products.

Even if issued, patents issued to us or our licensors may be challenged, narrowed, invalidated, held to be unenforceable or circumvented, which could limit our ability to stop competitors from marketing similar products or reduce the term of patent protection we may have for our products. We cannot assure you that any patents obtained will afford us adequate protection or provide us with any meaningful competitive advantages against these competitors.

Changes in either patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property or narrow the scope of our patent protection. For example, the America Invents Act was signed into law in the United States in September 2011, with phased implementation through March 2013, and includes a number of changes to established practices. These include the transition to a first-to-file system, establishment of new procedures for challenging patents and implementation of different methods for invalidating patents. We cannot predict the impact that new laws, government rule-making, implementing regulations and applicable case law may have on the strength of our patents. Certain reforms may make it easier for competitors to challenge our patents and could have a material adverse effect on our business and prospects. In addition, any patents we procure may require cooperation with companies holding related patents and we may have difficulty forming a successful relationship with such other companies.

If we are not able to adequately prevent disclosure of trade secrets and other proprietary information, the value of our product candidates could be significantly diminished.

We rely on trade secrets to protect our proprietary technologies, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, advisors, collaborators,

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and other third parties and partners to protect our trade secrets and other proprietary information. These agreements may not effectively prevent disclosure of confidential information or may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, third parties may independently develop or discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, currently is considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and any failure to obtain or maintain trade secret protection could adversely affect our competitive business position.

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

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to life sciences. This could make it difficult for us to stop the infringement of our in-licensed patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit.

Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate. In addition, changes in the law and legal decisions by courts in the United States and foreign countries may affect our ability to obtain adequate protection for our technology and the enforcement of intellectual property.

Confidentiality agreements with employees and others may not adequately prevent disclosure of trade secrets and other proprietary information.

In order to protect our proprietary technology and processes, we rely in part on confidentiality agreements with our corporate partners, employees, consultants, outside scientific collaborators and sponsored researchers and other advisors. These agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. In addition, others may independently discover trade secrets and proprietary information. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights, and failure to obtain or maintain trade secret protection could adversely affect our ability to successfully compete in the industry.

We may infringe the intellectual property rights of others, which may prevent or delay our product development efforts, prevent us from commercializing our products or increase the costs of commercializing our products.

Third parties may claim that we have infringed upon or misappropriated their proprietary rights. Third parties may attempt to obtain, patent protection relating to the production and use of our product candidates. We cannot assure you that any issued patents, or patents that may later issue to third parties, would not negatively affect our commercialization of ARIKAYCE, INS1009 or any other product. We cannot assure you that such patents can be avoided or invalidated or would be licensed to us at commercially reasonable rates or at all. We cannot assure you that we will be successful in any

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intellectual property litigation that may arise or that such litigation would not have an adverse effect on our business, financial condition, results of operation or prospects. In the event of a successful claim against us for infringement or misappropriation of a third party's proprietary rights, we may be required to:

- Pay damages, including up to treble damages, and the other party's attorneys' fees, which may be substantial;
- Cease the development, manufacture, marketing and sale of products or use of processes that infringe the proprietary rights of others;
- Expend significant resources to redesign our products or our processes so that they do not infringe the proprietary rights of others, which may not be possible;
- Redesign our products or processes to avoid third-party proprietary rights, which means we may suffer significant regulatory delays associated with conducting additional clinical trials or other steps to obtain regulatory approval; or
- Obtain one or more licenses arising out of a settlement of litigation or otherwise from third parties for the infringed proprietary rights, which may not be available to us on acceptable terms or at all.

Furthermore, litigation with any third party, even if the allegations are without merit, would likely be expensive and time-consuming and divert management's attention.

In particular, PAH is a competitive indication with established products, including other formulations of treprostinil. Our supply of the active pharmaceutical ingredient for INS1009 is dependent upon a single supplier. The supplier owns patents on its manufacturing process and we have filed patent applications for INS1009. A competitor in the PAH indication may claim that we or our supplier have infringed upon or misappropriated their proprietary rights. We cannot be sure that we or our supplier will be successful in any intellectual property litigation that may arise or that such litigation would not have an adverse effect on our business, financial condition, results of operation or prospects.

Any lawsuits relating to infringement of intellectual property rights necessary to defend ourselves or enforce our rights may be costly and time consuming.

Any conclusions we may have reached regarding non-infringement, inapplicability or invalidity of a third party's intellectual property are based in significant part on a review of publicly available databases and other information. There may be information not available to us or otherwise not reviewed by us that could change our conclusions. Moreover, the scope and validity of patent claims depend significantly on facts and circumstances, and a court's conclusions as to these matters may differ from the conclusions that we have reached.

We may have to undertake costly litigation to enforce any patents issued or licensed to us or to confirm the scope and validity of another party's proprietary rights. We cannot assure you that a court would validate our issued or licensed intellectual property. An adverse outcome in litigation or interference or other proceeding in any court or patent office could materially adversely affect our ability to develop and commercialize our product candidates.

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If we fail to comply with our obligations in our license agreements for our product candidates, we could lose license rights that are important to our business.

We currently have a licensing agreement with PARI for exclusive use of the optimized eFlow Nebulizer System for delivery of ARIKAYCE in treating patients with NTM infections, CF and bronchiectasis. We have rights to several US and foreign issued patents, and patent applications involving improvements to the optimized eFlow Nebulizer System. Under the licensing agreement, PARI is entitled to receive payments either in cash, qualified stock or a combination of both, at PARI's discretion, based on achievement of certain milestone events including phase 3 trial initiation, first acceptance of MAA submission (or equivalent) in the US of ARIKAYCE and the device, first receipt of marketing approval in the US for ARIKAYCE and the device, and first receipt of marketing approval in a major EU country for ARIKAYCE and the device. There can be no assurance that the foregoing milestone events will be achieved and therefore there can be no assurance that we will make any future payments. We are required to use commercially reasonable efforts to pursue the clinical development of ARIKAYCE in one or more countries and, for CF at least in the United States, and after obtaining such marketing approval to use commercially reasonable efforts to market and sell ARIKAYCE in the countries in which it is approved. If we fail to meet some or all of our obligations under the licensing agreement or choose to discontinue commercialization of ARIKAYCE in any indication, PARI may compete in the indication, we may lose the exclusive rights to use the PARI device with ARIKAYCE in the indication, and we may lose the non-exclusive right to use the PARI device with ARIKAYCE in the indication. Termination of the licensing agreement or loss of exclusive rights may occur if we fail to meet our obligations, including payment of royalties to PARI, or if we do not meet certain milestones contained in the licensing agreement such as obtaining marketing approval or achieving the first commercial sale of ARIKAYCE. PARI may also choose to terminate the agreement if we do not use commercially reasonable efforts over a two year period of time.

Risks Related to Our Industry

We operate in a highly competitive and changing environment, and if we are unable to adapt to our environment, we may be unable to compete successfully.

Biotechnology and related pharmaceutical technology have undergone and are likely to continue to experience rapid and significant change. We expect that the technologies associated with biotechnology research and development will continue to develop rapidly. Our future success will depend in large part on our ability to maintain a competitive position with respect to these technologies and to obtain and maintain protection for our intellectual property. Any compounds, products or processes that we develop may become obsolete before we recover any expenses incurred in connection with their development. Rapid technological change could make our products obsolete, and materially adversely affect our business, financial condition, results of operations or prospects.

We expect that successful competition will depend, among other things, on product efficacy, safety, reliability, availability, timing and scope of regulatory approval and price. Specifically, we expect crucial factors will include the relative speed with which we can develop products, complete the clinical testing and regulatory approval processes and supply commercial quantities of the product to the market. We expect competition to increase as technological advances are made and commercial applications broaden.

In each of our potential product areas, we face substantial competition from pharmaceutical, biotechnology and other companies, universities and research institutions. Relative to us, most of these entities have substantially greater capital resources, research and development staffs, facilities and experience in conducting clinical studies and obtaining regulatory approvals, as well as in manufacturing

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and marketing pharmaceutical products. Many of our competitors may achieve product commercialization or patent protection earlier than us. Furthermore, we believe that our competitors have used, and may continue to use, litigation to gain a competitive advantage. Finally, our competitors may use different technologies or approaches to the development of products similar to the products we are seeking to develop.

If ARIKAYCE is approved for *Pseudomonas* lung infections in CF patients, it will compete against Tobi, the current standard of care for the chronic management of these infections. Tobi is marketed by Novartis. Other competitors in this market include Gilead and Actavis, and we are aware of other companies also developing products for this indication. We cannot assure you that if ARIKAYCE is approved for this indication or NTM that it will be able to compete successfully in the marketplace.

Competitors could develop and obtain FDA approval of products containing amikacin, which could adversely affect our competitive position in all ARIKAYCE-related indications.

In the event there are other amikacin products approved by the FDA for any use, physicians may elect to prescribe those products rather than ARIKAYCE to treat the indications for which ARIKAYCE may receive approval, which is commonly referred to as off-label use. Although FDA regulations prohibit a drug company from promoting off-label use of its product, the FDA does not regulate the practice of medicine and as a result cannot direct physicians as to what product to prescribe to their patients. As a result, we would have limited ability to prevent any off-label use of a competitor's product to treat diseases for which we have received FDA approval, even if such use violates our patents or orphan drug exclusivity for the use of amikacin to treat such diseases. This could negatively affect our results of operations or business.

Competitors could develop and obtain FDA approval of antibiotic products that are more effective, safer, tolerable or more convenient or less expensive than our products in development or existing products, which could adversely affect our competitive position in all ARIKAYCE-related indications.

There are potential competitive products, both approved and in development, which include oral, systemic, or inhaled antibiotic products to treat chronic respiratory infections. If any of our competitors develops a product that is more effective, safer, tolerable or, convenient or less expensive than ARIKAYCE, it would adversely affect our ability to generate revenues. We also may face lower priced generic competitors if third-party payers encourage use of generic or lower-priced versions of our product or if competing products are imported into the US from Canada, Mexico or other countries.

Regulatory approvals of products that treat the underlying cause of CF could reduce the market opportunity for ARIKAYCE.

The FDA and EMA have approved Kalydeco (ivacaftor) by Vertex as the first drug approved to treat patients with certain mutations of CF. Vertex also is studying Kalydeco, in combination with another drug candidate, for a more common CF mutation. We cannot predict the potential effects of Kalydeco or similar products approved in the future on inhaled antibiotic use in CF. It is possible that these therapies could decrease the number or proportion of CF patients who acquire *Pseudomonas* lung infections and thereby decrease the market for inhaled antibiotics like ARIKAYCE.

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If another party obtains orphan drug exclusivity for a product that is essentially the same as a product we are developing for a particular indication, we may be precluded or delayed from commercializing the product in that indication.

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the US. See "Business Government Regulation Orphan Drugs United States." The company that obtains the first marketing approval from the FDA for a designated orphan drug for a rare disease receives marketing exclusivity for use of that drug for the designated condition for a period of seven years. Similar laws exist in EU with a term of ten years. See "Business Government Regulation Orphan Drugs Europe." If a competitor obtains approval of the same drug for the same indication or disease before us, we would be prohibited from obtaining approval for our product for seven or more years, unless our product can be shown to be clinically superior. In addition, more than one drug may be approved by the FDA for the same orphan indication or disease as long as the drugs are different drugs. As a result, even if one of our products is approved and receives orphan drug exclusivity, as ARIKAYCE was for treating patients with NTM infections and CF patients with *Pseudomonas*, the FDA may approve different drugs for use in treating the same indication or disease covered by our product, which could adversely affect our competitive position.

If we obtain orphan exclusivity for a product, the FDA may approve another product during our orphan exclusivity period for the same indication under certain circumstances.

The Orphan Drug Act was created to encourage companies to develop therapies for rare diseases by providing incentives for drug development and commercialization. One of the incentives provided by the act is seven years of market exclusivity in the United States for the first product in a class licensed for the treatment of a rare disease. Orphan exclusivity will not, however, bar approval of another product under certain circumstances. One such circumstance is if a product with the same active ingredient is proven safe and effective for a different indication. Another circumstance is if a subsequent product with the same active ingredient for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care. FDA may also approve another product with the same active ingredient and the same indication if the company with orphan drug exclusivity is not able to meet market demand. Further, FDA may approve more than one product for the same orphan indication or disease as long as the products contain different active ingredients. As a result, even if one of our product candidates receives orphan exclusivity, the FDA can still approve other drugs that have a different active ingredient for use in treating the same indication or disease. All of the above circumstances could create a more competitive market for us.

Our research, development and manufacturing activities used in the production of ARIKAYCE involve the use of hazardous materials, which could expose us to damages and materially adversely affect our results of operations and financial condition.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our research and development program and manufacturing activities for ARIKAYCE involve the controlled use of hazardous materials and chemicals. We generally contract with third parties for the disposal of these materials and wastes. Although we believe we are in compliance with all pertinent regulations, we cannot eliminate the risk of environmental contamination, damage to facilities or injury to personnel from the accidental or improper use or control of these materials. In addition to any liability we could have for any misuse by us of hazardous materials and chemicals, we could also potentially be liable for activities of our contract manufacturers or other third

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parties. Any such liability, or even claims of such liability, could materially adversely affect our results of operations and financial condition. We also could incur significant costs associated with civil or criminal fines and penalties.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

We may be subject to product liability claims, and we have only limited product liability insurance.

The manufacture and sale of human therapeutic products involve an inherent risk of product liability claims and associated adverse publicity. We currently have only limited product liability insurance for our products. We do not know if we will be able to maintain existing or obtain additional product liability insurance on acceptable terms or with adequate coverage against potential liabilities. This type of insurance is expensive and may not be available on acceptable terms. If we are unable to obtain or maintain sufficient insurance coverage on reasonable terms or to otherwise protect against potential product liability claims, we may be unable to commercialize our products. A successful product liability claim brought against us in excess of our insurance coverage, if any, may require us to pay substantial amounts and may materially adversely affect our business, financial condition, results of operations or prospects.

Risks Related to Employee Matters and Managing Growth

We are dependent upon retaining and attracting key personnel, the loss of whose services could materially adversely affect our business, financial condition, results of operations and prospects.

We depend highly on the principal members of our scientific and management personnel, the loss of whose services might significantly delay or prevent the achievement of our research, development or business objectives. Our success depends, in large part, on our ability to attract and retain qualified management, scientific and medical personnel, and on our ability to develop and maintain important relationships with commercial partners, leading research institutions and key distributors. We will need to hire additional personnel in anticipation of seeking regulatory approval for and commercial launch of ARIKAYCE.

Competition for skilled personnel in our industry and market is very intense because of the numerous pharmaceutical and biotechnology companies that seek similar personnel. These companies may have greater financial and other resources, offer a greater opportunity for career advancement and have a longer history in the industry than we do. We also experience competition for the hiring of our scientific and clinical personnel from universities, research institutions, and other third parties. We cannot assure that we will attract and retain such persons or maintain such relationships.

Our inability to retain and attract qualified employees would harm our business.

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

We expect that our potential expansion into areas and activities requiring additional expertise, such as further clinical trials, governmental approvals, manufacturing, sales, marketing and distribution will place additional requirements on our management, operational and financial resources. Future growth would impose significant added responsibilities on members of management, including the need

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to identify, recruit, maintain, motivate and integrate additional employees. Also, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees.

The anticipated commercialization of ARIKAYCE and the development of additional product candidates will require significant expenditures by us and place a strain on our resources. If our management is unable to effectively manage our activities in anticipation of commercialization, as well as our development efforts, we may incur higher than expected expenditures or other expenses and our business may otherwise be adversely affected.

Risks Related to our Common Stock and Listing on the Nasdaq Global Select Market

The market price of our stock has been and may continue to be highly volatile.

Our common stock is listed on the Nasdaq Global Select Market under the ticker symbol INSM. The market price of our stock has been and may continue to be highly volatile, and could be subject to wide fluctuations in price in response to various factors, many of which are beyond our control. These factors may include:

- Our listing status on the Nasdaq Global Select Market;
- Results of our clinical studies and preclinical studies, or those of our corporate partners or our competitors;
- Delays in timing of pre-clinical, clinical development and regulatory filings and delays regarding our inability to obtain potential approvals;
- Strategic business decisions;
- Developments in our relationships with corporate partners;
- Developments affecting our corporate partners;
- Negative regulatory action or regulatory approval with respect to our announcement or our competitors' announcements of new products;
- Government regulation, reimbursement changes and governmental investigation or audits related to us or to our products;
- Developments related to our patents or other proprietary rights or those of our competitors;
- Other competitive developments;
- Reports issued by and changes in the position of securities analysts with respect to our stock or changes in stock ownership by investors;
- Operating results below the expectations of securities analysts and investors; and
- The need or perceived need to raise additional capital.

In addition, the stock market has from time to time experienced extreme price and volume fluctuations, which have particularly affected the market prices for emerging biotechnology and pharmaceutical companies like us, and which have often been unrelated to their operating performance. These broad market fluctuations may adversely affect the market price of our common stock.

Historically, when the market price of a stock has been volatile, shareholders are more likely to institute securities and derivative class action litigation against the issuer of such stock. If any of our shareholders were to institute a lawsuit against us, we could incur substantial costs defending the lawsuit. Any lawsuit could divert the time and attention of our management.

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Future sales of substantial amounts of common stock in the public market, or the possibility of such sales occurring, could also adversely affect prevailing market prices for our common stock or our future ability to raise capital through an offering of equity securities.

The sale of a significant number of shares of our common stock in the public market could harm the market price of our common stock. The market price for our common stock could also decline, perhaps significantly, as a result of issuances of a large number of shares of our common stock in the public market or even the perception that such issuances could occur.

If we fail to meet the continued listing requirements of the Nasdaq Global Select Market, our common stock may be delisted from the Nasdaq Global Select Market, which may cause the value of an investment in our common stock to decrease.

If a delisting from the Nasdaq Global Select Market were to occur, our common stock may be eligible, upon the application of a market maker, to trade on the OTC Bulletin Board or in the "pink sheets." These alternative markets are generally considered to be less efficient than, and not as broad as, the Nasdaq Global Select Market. Therefore, delisting of our common stock from the Nasdaq Global Select Market could adversely affect the trading price of our common stock and could limit the liquidity of our common stock and therefore could cause the value of an investment in our common stock to decrease.

The ownership interest of existing shareholders will be diluted by the exercise of options issued by us or to the extent that we issue additional common stock in connection with any offerings of securities, strategic transactions, or otherwise.

As of February 2, 2015, 4,763,528 shares of our common stock are potentially issuable under outstanding restricted stock units and stock options to our employees, officers, directors and consultants.

The conversion or exercise of some or all of our restricted stock units and options will dilute the ownership interests of existing shareholders. Any sales in the public market of the common stock issuable upon such conversion or exercise could adversely affect prevailing market prices of our common stock.

Additionally, our Articles of Incorporation currently authorize us to issue up to 500 million common shares. As of February 2, 2015 we had 49,994,137 shares of common stock outstanding. To the extent that we issue additional common stock in connection with any offerings of securities, strategic transactions, or otherwise, the ownership interest of existing shareholders will be further diluted.

Historically we have not paid dividends on our common stock, and we have no plans to pay dividends in the foreseeable future.

We have never declared or paid any cash dividend on our common stock and do not currently intend to do so for the foreseeable future. We currently anticipate that we will retain any future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which our stockholders have purchased their shares.

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Certain provisions of Virginia law and our articles of incorporation and amended and restated bylaws could hamper a third party's acquisition of, or discourage a third party from attempting to acquire control of us.

Certain provisions of Virginia law and our articles of incorporation and amended and restated bylaws could hamper a third party's acquisition of, or discourage a third party from attempting to acquire control of us or limit the price that investors might be willing to pay for shares of our common stock. These provisions include:

- A provision allowing us to issue preferred stock with rights senior to those of the common stock without any further vote or action by the holders of the common stock. The issuance of preferred stock could decrease the amount of earnings and assets available for distribution to the holders of common stock or could adversely affect the rights and powers, including voting rights, of the holders of the common stock. In certain circumstances, such issuance could have the effect of decreasing the market price of the common stock;
- The existence of a staggered board of directors in which there are three classes of directors serving staggered three-year terms, thus expanding the time required to change the composition of a majority of directors and perhaps discouraging someone from making an acquisition proposal for us;
- Our amended and restated bylaws' requirement that shareholders provide advance notice when nominating director candidates to serve on our Board of Directors;
- The inability of shareholders to convene a shareholders' meeting without the chairman of the board, the president or a majority of the board of directors first calling the meeting; and
- The application of Virginia law prohibiting us from entering into a business combination with the beneficial owner of 10% or more of our outstanding voting stock for a period of three years after the 10% or greater owner first reached that level of stock ownership, unless we meet certain criteria.

In addition, we previously had a "poison pill" shareholder rights plan, which expired in May 2011. Under Virginia law, our Board of Directors may implement a new shareholders rights plan without shareholder approval. Our Board of Directors intends to regularly consider this matter, even in the absence of specific circumstances or takeover proposals, to facilitate its future ability to quickly and effectively protect shareholder value.

Other Risks Related to our Business

Corporate governance and public disclosure requirements add uncertainty to our compliance policies and increase our costs of compliance.

Changing laws, regulations and standards relating to accounting, corporate governance and public disclosure, including the Sarbanes-Oxley Act of 2002, other SEC regulations, and the Nasdaq Global Select Market rules, are creating uncertainty for companies like ours. These laws, regulations and standards may lack specificity and are subject to varying interpretations. Their application in practice may evolve over time, as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs of compliance as a result of ongoing revisions to such corporate governance standards.

In particular, our efforts to comply with Section 404 of the Sarbanes-Oxley Act of 2002, to furnish a report by management on, among other things, the effectiveness and the related regulations regarding our required assessment of our internal controls over financial reporting and our external auditors' audit of our internal control over financial reporting requires the commitment of significant financial and managerial resources. We consistently assess the adequacy of our internal controls over

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financial reporting, remediate any control deficiencies that may be identified, and validate through testing that our controls are functioning as documented. While we do not anticipate any material weaknesses, the inability of management and our independent auditor to provide us with an unqualified report as to the effectiveness of our internal controls over financial reporting for future year ends could result in adverse consequences to us, including, but not limited to, a loss of investor confidence in the reliability of our financial statements, which could cause the market price of our stock to decline. For example, in connection with our review of internal control over financial reporting as of December 31, 2012, we determined that we did not adequately implement certain controls over the administration, accounting and oversight of our 2000 Stock Incentive Plan, and we concluded that a material weakness in our internal control over financial reporting existed as of December 31, 2012. The existence of this or one or more other material weaknesses or significant deficiencies in our internal control over financial reporting could result in errors in our financial statements, and substantial costs and resources may be required to rectify any internal control deficiencies. Any material weaknesses may materially adversely affect our ability to report accurately our financial condition and results of operations in a timely and reliable manner. In addition, although we continually review and evaluate internal control systems to allow management to report on the sufficiency of our internal controls, we cannot assure you that we will not discover weaknesses in our internal control over financial reporting. Any such weakness or failure to remediate a material weakness could materially adversely affect our ability to comply with applicable financial reporting requirements and the requirements of our various agreements.

We are committed to maintaining high standards of corporate governance and public disclosure, and our efforts to comply with evolving laws, regulations and standards in this regard have resulted in, and are likely to continue to result in, increased general and administrative expenses and a diversion of management time and attention from revenue-generating activities to compliance activities. In addition, the laws, regulations and standards regarding corporate governance may make it more difficult for us to obtain director and officer liability insurance. Further, our board members, chief executive officer and chief financial officer could face an increased risk of personal liability in connection with their performance of duties. As a result, we may face difficulties attracting and retaining qualified board members and executive officers, which could harm our business. If we fail to comply with new or changed laws, regulations or standards of corporate governance, our business and reputation may be harmed.

Our internal computer systems, or those of our CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our business operations, including our drug development programs.

Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could result in a material adverse effect on our business operations, including a material disruption of our drug development programs. Unauthorized disclosure of sensitive or confidential client or employee data, whether through breach of computer systems, systems failure, employee negligence, fraud or misappropriation, or otherwise, could damage our reputation. Similarly, unauthorized access to or through our information systems and networks, whether by our employees or third parties, could result in negative publicity, legal liability and damage to our reputation. For example, the loss of clinical trial data from completed or ongoing clinical trials for any of our drug candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach was to result in a loss of or damage to our data or applications, or

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inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our drug candidates could be delayed.

Although we have general liability insurance coverage, including coverage for errors or omissions, there can be no assurance that our coverage will cover all claims, continue to be available on reasonable terms or will be sufficient in amount to cover one or more large claims, or that the insurer will not disclaim coverage as to any future claim. The successful assertion of one or more large claims against us that exceed or are not covered by our insurance coverage or changes in our insurance policies, including premium increases or the imposition of large deductible or co-insurance requirements, could have a material adverse effect on our business, results of operations and financial condition.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

We currently lease 42,857 square feet of laboratory and office space at 10 Finderne Avenue in Bridgewater, New Jersey. This lease will expire in November 2019. We have the ability to lease approximately 14,000 square feet of additional space at this location.

We also lease approximately 18,000 square feet of office space in Richmond, Virginia. The lease expires in October 2016. Our corporate headquarters were formerly located in Richmond but we closed this facility. In December 2014, we entered into an agreement to sublet this space for the remainder of the lease term.

ITEM 3. LEGAL PROCEEDINGS

From time to time, we are a party to various lawsuits, claims and other legal proceedings that arise in the ordinary course of our business. While the outcomes of these matters are uncertain, management does not expect that the ultimate costs to resolve these matters will have a material adverse effect on our consolidated financial position, results of operations or cash flows. See Note 11 to the Notes to the Consolidated Financial Statements included in this report for a description of our current legal proceedings.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

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PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Our trading symbol is "INSM." Our common stock currently trades on the Nasdaq Global Select Market. Until February 3, 2014, our common stock traded on the Nasdaq Capital Market. The following table lists the high and low sale prices per share for our common stock on a quarterly basis for both 2014 and 2013.

Fiscal Year 2014	**High**	**Low**
Fourth Quarter	$ 16.42	$ 12.57
Third Quarter	20.11	11.65
Second Quarter	19.98	12.10
First Quarter	21.54	15.91

Fiscal Year 2013	**High**	**Low**
Fourth Quarter	$ 17.60	$ 12.17
Third Quarter	16.50	9.00
Second Quarter	14.30	6.56
First Quarter	7.71	5.56

On February 2, 2015, the last reported sale price for our common stock on the Nasdaq Global Select Market was $15.41 per share. As of February 2, 2015, there were 143 holders of record of our common stock.

On December 15, 2014, we entered into a Stock Purchase Agreement with Hercules pursuant to which we issued 70,771 shares of common stock, par value $0.01 per share (which represented less than 1% of the outstanding Common Stock as of the date thereof), at a price of $14.13 per share (the closing price on December 12, 2014), for an aggregate purchase price of approximately $1.0 million. The securities sold in the private placement were not registered under the Securities Act of 1933, as amended (the "Act") and may not be offered or sold in the United States in the absence of an effective registration statement or exemption from the registration requirements under the Act. We believe that the issuance of the securities in this transactions were exempt from registration under Section 4(2) of the Act.

We have never declared or paid cash dividends on our common stock. We anticipate that we will retain all earnings, if any, to support operations and to finance the growth and development of our business for the foreseeable future. Therefore, we do not currently expect to pay cash dividends from earnings. Any future determination as to the payment of dividends will be at the sole discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors our board of directors deems relevant, as well as any contractual or other restrictions to which we may be subject.

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COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN*
Among Insmed Incorporated, the NASDAQ Composite Index, the S&P 500 Index, the NASDAQ Pharmaceutical Index and the NASDAQ Biotechnology Index

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* $100 invested on 12/31/09 in stock or index, including reinvestment of dividends.
Fiscal year ending December 31.

ITEM 6. SELECTED FINANCIAL DATA

The following selected financial data reflects our consolidated statements of operations and consolidated balance sheets as of and for the years ended December 31, 2014, 2013, 2012, 2011 and 2010. The data below should be read in conjunction with, and is qualified by reference to, "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our

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consolidated financial statements and notes thereto contained elsewhere in this Annual Report on Form 10-K.

	Year Ended December 31,				
	2014	2013	2012	2011	2010
	(in thousands, except per share data)				
Historical Statement of Operations Data:					
Revenues	$ -	$ 11,500	$ -	$ 4,417	$ 6,921
Operating expenses:					
Research and development	56,292	44,279	29,781	28,623	4,702
General and administrative	31,073	22,236	12,657	11,523	10,311
Impairment loss	-	-	-	25,990	-
Total operating expenses	87,365	66,515	42,438	66,136	15,013
Operating loss	(87,365)	(55,015)	(42,438)	(61,719)	(8,092)
Investment income	58	166	1,822	2,064	1,845
Interest expense	(2,415)	(2,412)	(763)	(10)	(109)
Other, net	141	(33)	5	1	-
Loss before income taxes	(89,581)	(57,294)	(41,374)	(59,664)	(6,356)
Income tax (benefit)/expense	(10,422)	(1,221)	-	-	78
Net loss	(79,159)	(56,073)	(41,374)	(59,664)	(6,434)
Accretion of beneficial conversion feature	-	-	-	(9,175)	-
Net loss attributable to common stockholders	$ (79,159)	$ (56,073)	$ (41,374)	$ (68,839)	$ (6,434)
Basic and diluted net loss attributable to common stockholders per share (1)	$ (1.84)	$ (1.60)	$ (1.56)	$ (2.95)	$ (0.49)
Weighted average basic and diluted common shares outstanding (1)	43,095	34,980	26,545	23,348	13,250
Historical Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 159,226	$ 113,894	$ 90,782	$ 76,272	$ 108,049
Certificate of deposit	$ -	$ -	$ 2,153	$ 2,085	$ 2,176
Total assets	$ 230,864	$ 176,498	$ 153,561	$ 139,833	$ 196,265
Current portion of long-term debt	$ -	$ 3,283	$ 3,007	$ -	$ -
Long-term debt, net of current portion	$ 24,856	$ 16,338	$ 16,221	$ -	$ -
Stockholders' equity	$ 186,237	$ 143,324	$ 120,882	$ 134,267	$ 192,843

(1) During the first quarter of 2011, our board of directors authorized a one-for-ten reverse stock split. All share and per share amounts included in the above selected financial data give retroactive effect to the one-for-ten stock split for all periods presented.

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ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion also should be read in conjunction with our consolidated financial statements and the notes thereto.

OVERVIEW

Insmed is a biopharmaceutical company dedicated to improving the lives of patients battling serious lung diseases. We are focused on the development and commercialization of ARIKAYCE, or liposomal amikacin for inhalation, for at least two identified orphan patient populations: patients with nontuberculous mycobacteria (NTM) lung infections and cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* (*Pseudomonas)* lung infections. We are also focused on the development of INS1009, an inhaled treprostinil prodrug. Treprostinil is a prostacyclin used in the treatment of pulmonary arterial hypertension (PAH), a chronic, life-threatening disorder characterized by abnormally high blood pressure in the arteries between the heart and lungs.

In the fourth quarter of 2014, we filed a Marketing Authorization Application (MAA) with the EMA for ARIKAYCE for the treatment of NTM lung infections as well as *Pseudomonas*lung infections in CF patients. The MAA for ARIKAYCE was validated in February 2015 after the EMA's pediatric committee approved the Pediatric Investigation Plan (PIP) for ARIKAYCE. The validation of the MAA filing is the start of the formal review process by the EMA.

In addition, following discussions with the FDA, we have commenced a phase 3 randomized, open-label, global study which is designed to confirm the positive culture conversion results seen in our phase 2 clinical trial. This confirmatory study is investigating ARIKAYCE for use in non-CF patients 18 years and older with *Mycobacterium avium* complex (MAC) NTM lung infections who have thus far failed to achieve culture conversion on a multi-drug treatment regimen. This subgroup of patients in the phase 2 trial responded particularly well to treatment. We believe this approach will confirm the previous study results and could provide a path to filing and approval for an indication in patients with NTM who are refractory to treatment. Following discussions with the FDA, the primary efficacy endpoint will be proportion of patients achieving culture conversion, with additional goals of demonstrating sustainability and safety. The protocol for the phase 3 trial was agreed upon following dialogue with the FDA and was approved by the U.S. Central Institutional Review Board (IRB). We initiated the global trial in early 2015 and expect to complete enrollment within one year. We anticipate having preliminary top-line clinical results from the confirmatory phase 3 study in mid-2016. If the study meets the primary endpoint of culture conversion, we believe we would be eligible to submit a new drug approval application (NDA) pursuant to 21 CFR 314 Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) which permits FDA to approve a drug based on a "surrogate endpoint" provided the sponsor commits to post-market studies to verify and describe the drug's clinical benefit. We expect to conduct the trial at over eighty sites including the United States, Europe, Australia, Japan and Canada with enrollment of approximately 300 patients.

We were incorporated in the Commonwealth of Virginia on November 29, 1999. On December 1, 2010, we completed a business combination with Transave, Inc., a privately held, New Jersey-based pharmaceutical company focused on the development of differentiated and innovative inhaled pharmaceuticals for the site-specific treatment of serious lung infections. Our continuing operations are based on the technology and products historically developed by Transave. Our principal executive offices are located at 10 Finderne Avenue, Building 10, Bridgewater, New Jersey 08807 and our phone number is (908) 977-9900. Our Internet address is www.insmed.com.

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KEY COMPONENTS OF OUR STATEMENT OF OPERATIONS

Revenues

We did not recognize any revenue in 2014 and 2012. In 2013, our other revenue solely consisted of an $11.5 million payment received from Premacure Holdings AB and Premacure AB of Sweden (now Shire plc) in exchange for the Company's right to receive royalties under its license agreement with Premacure. We recorded this as other revenue after all four revenue recognition criteria were present and we had no continuing performance obligations related to the payment received. We currently do not recognize any revenue from product sales or other sources.

Research and Development Expenses

Research and development expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our research and development functions, and other internal operating expenses, the cost of manufacturing our drug candidate for clinical study, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. Our expenses related to manufacturing our drug candidate for clinical study are primarily related to activities at contract manufacturing organizations that manufacture ARIKAYCE for our use. Our expenses related to clinical trials are primarily related to activities at contract research organizations that conduct and manage clinical trials on our behalf. These contracts set forth the scope of work to be completed at a fixed fee or amount per patient enrolled. Payments under these contracts primarily depend on performance criteria such as the successful enrollment of patients or the completion of clinical trial milestones as well as time-based fees. Expenses are accrued based on contracted amounts applied to the level of patient enrollment and to activity according to the clinical trial protocol. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized. Such amounts are then recognized as an expense as the related goods are delivered or the services are performed, or when the goods or services are no longer expected to be provided.

Since 2011, we have focused our development activities principally on our proprietary, advanced liposomal technology designed specifically for inhalation lung delivery. In 2013, we completed a phase 3 trial in Europe and Canada in which we evaluated ARIKAYCE in CF patients with Pseudomonas lung infections. In 2014, we completed a phase 2 clinical trial in the US and Canada of ARIKAYCE in patients with NTM lung infections. In 2015, we commenced a global phase 3 trial for ARIKAYCE for patients with NTM lung infections. We are also conducting an open label extension study in which CF patients that completed our phase 3 trial receive ARIKAYCE for a period of two years. Since our business combination with Transave, the majority of our research and development expenses have been for our ARIKAYCE program. Our development efforts in 2015 principally relate to the development of ARIKAYCE in the NTM indication and, to a lesser extent, for INS1009 for PAH.

Our clinical trials are subject to numerous risks and uncertainties that are outside of our control, including the possibility that necessary regulatory approvals may not be obtained. In addition, the duration and the cost of clinical trials may vary significantly from trial to trial over the life of a project as a result of differences in the study protocol for each trial as well as differences arising during the clinical trial, including, among others, the following:

- The number of patients that ultimately participate in the trial;
- The duration of patient follow-up that is determined to be appropriate in view of results;
- The number of clinical sites included in the trials;
- The length of time required to enroll suitable patient subjects; and

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- The efficacy and safety profile of the product candidate.

Our clinical trials may be subject to delays, particularly if we are unable to produce clinical trial material in sufficient quantities and of sufficient quality to meet the schedule for our clinical trials. Moreover, all of our product candidates must overcome significant regulatory, technological, manufacturing and marketing challenges before they can be successfully commercialized. Any significant delays that occur or additional expenses that we incur may have a material adverse effect on our financial position and may require us to raise additional capital sooner or in larger amounts than is presently expected. In addition, as a result of the risks and uncertainties related to the development and approval of our product candidates and the additional uncertainties related to our ability to market and sell these products once approved for commercial sale, we are unable to provide a meaningful prediction regarding when, if at all, we will generate positive cash inflow from these projects.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our executive, finance and accounting, legal, pre-commercial, corporate development, information technology, program management and human resource functions. General and administrative expenses also include professional fees for legal, including patent-related expenses, consulting, insurance, board of director fees, tax and accounting services. We expect that our general and administrative expenses will increase in order to support increased levels of development activities and commencement of commercialization activities for our product candidates.

Debt Issuance Costs

Debt issuance costs are amortized to interest expense using the effective interest rate method over the term of the debt. Our balance sheet reflects debt net of debt issuance costs paid to the lender and reflects debt issuance costs paid to other third parties as other assets.

Investment Income and Interest Expense

Investment income consists of interest and dividend income earned on our cash, cash equivalents and short-term investments, along with realized gains (losses) on the sale of investments. Interest expense consists primarily of interest costs related to our debt and capital lease obligations.

RESULTS OF OPERATIONS

Comparison of the Years Ended December 31, 2014 and 2013

Net Loss

Net loss for the year ended December 31, 2014 was $79.2 million, or ($1.84) per common share basic and diluted, compared with a net loss of $56.1 million, or ($1.60) per common share basic and diluted for the year ended December 31, 2013. The $23.1 million increase in our net loss in the year ended December 31, 2014 as compared to 2013 was primarily due to $11.5 million in Other revenue received in 2013 related to a one-time payment for the sale of the Company's right to receive future royalties under its license agreement with Premacure (now Shire plc). An increase in 2014 expenses also contributed to the increase in net loss for the period and included an:

- $12.0 million increase in our research and development expenses that primarily resulted from an increase in manufacturing expenses as a result of the build-out of a production area at

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Therapure's facility, the completion of certain process improvement projects at our third party manufacturing partner and the manufacture of ARIKAYCE for clinical supply. In addition, there was an increase in internal expenses, specifically compensation and personnel related expenses, including non-cash stock compensation expense. These increases were offset, in part, by a decrease in external clinical expenses which was primarily related to the fact that our phase 3 pivotal study in CF patients was completed in 2013; and

- $8.9 million increase in our general and administrative expenses resulted from an increase in pre-commercial expenses and an increase in certain administrative expenses including an increase in headcount and related compensation expenses and an increase in expenses related to our new headquarters and laboratory facilities in Bridgewater, New Jersey.

Partially offsetting these expenses was a $9.2 million increase in the benefit from income taxes resulting from the sale of a portion of our New Jersey State NOLs under the State of New Jersey's Technology Business Tax Certificate Transfer Program for cash of $10.4 million and $1.2 million in 2014 and 2013, respectively, net of commissions. The $10.4 million of benefit from income taxes represents two years of sales of NOLs, one in January 2014 and one in December 2014.

Other Revenue

Other revenue in 2013 solely consisted of a one-time $11.5 million payment we received from Premacure (now Shire plc) in exchange for the Company's right to receive future royalties under its license agreement with Premacure (see Note 10 to the consolidated financial statements on Form 10-K for the year ended December 31, 2014 for additional information regarding our agreement with Premacure). We recorded this as Other revenue in 2013, since all revenue recognition criteria were met and we had no continuing performance obligations related to the payment received.

Research and Development Expenses

Research and development expenses for the year ended December 31, 2014 and 2013 comprised the following:

	Years Ended December 31,		Increase (Decrease)	
	2014	2013	$	%
External Expenses				
Clinical development & research	$ 12,327	$ 19,728	$ (7,401)	-37.5%
Manufacturing	16,320	7,906	8,414	106.4%
Regulatory and quality assurance	4,888	2,010	2,878	143.2%
Subtotal external expenses	$ 33,535	$ 29,644	$ 3,891	13.1%
Internal Expenses				
Compensation and related expenses	$ 17,543	$ 10,327	$ 7,216	69.9%
Other internal operating expenses	5,214	4,308	906	21.0%
Subtotal internal expenses	$ 22,757	$ 14,635	$ 8,122	55.5%
Total	$ 56,292	$ 44,279	$ 12,013	27.1%

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Research and development expenses increased to $56.3 million during the year ended December 31, 2014 from $44.3 million in the same period in 2013. The $12.0 million increase was primarily due to a $8.4 million increase in manufacturing expenses as a result of the build-out of a production area at Therapure's facility, the completion of certain process improvement projects at our third party manufacturing partner, and the manufacture of ARIKAYCE for clinical supply. In addition, there was a $8.1 million increase in internal expenses, specifically a $7.2 million increase in compensation and related expenses, which included an increase of $2.2 million in stock compensation expenses and additional expenses related to the transition and consulting agreement with our former chief medical officer. These increases were offset, in part, by a decrease of $7.4 million in external clinical expenses which was primarily related to the fact that our phase 3 pivotal study in CF patients was completed in 2013. We expect research & development expenses to increase in 2015 as compared to 2014 due primarily to the clinical trial activity related to our global phase 3 study which is expected to complete enrollment within the next twelve months and also for research expenses related to our INS1009 program for PAH.

General and Administrative Expenses

General and administrative expenses for the years ended December 31, 2014 and 2013 comprised the following:

	December 31,		Increase (Decrease)	
	2014	2013	$	%
General & administrative	$ 23,032	$ 18,627	$ 4,405	23.6%
Pre-commercial expenses	8,041	3,609	4,432	122.8%
Total general & administrative expenses	$ 31,073	$ 22,236	$ 8,837	39.7%

General and administrative expenses increased to $31.1 million during the year ended December 31, 2014 from $22.2 million in the same period in 2013. The $8.9 million increase was primarily due to a $4.5 million increase in pre-commercial expenses and an increase in certain administrative expenses including a $1.8 million increase in headcount and related compensation expense and a $1.5 million increase in expenses related to our new headquarters and laboratory facilities in Bridgewater, New Jersey. We expect general and administrative expenses to increase in 2015 as compared to 2014 due, in part, to an increase in expenditures related to commercial readiness activities in certain European markets.

Investment Income and Interest Expense

Investment income was $0.1 million and $0.2 million during the years ended December 31, 2014 and 2013, respectively. Interest expense was $2.4 million during the years ended December 31, 2014 and 2013 and represents interest expense under our Loan Agreement.

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Benefit from Income Taxes

The benefit for income taxes was $10.4 million and $1.2 million for the years ended December 31, 2014 and 2013, respectively. The benefit for income taxes recorded for the years ended December 31, 2014 and 2013 solely reflect the reversal of a valuation allowance previously recorded against our New Jersey State net operating losses (NOLs) that resulted from the sale of a portion of our New Jersey State NOLs under the State of New Jersey's Technology Business Tax Certificate Transfer Program (the "Program") for cash of $10.4 million and $1.2 million, respectively and net of commissions. The Program allows qualified technology and biotechnology businesses in New Jersey to sell unused amounts of NOLs and defined research and development tax credits for cash. The $10.4 million of benefit from income taxes represents two years of sales of NOLs, one in January 2014 and one in December 2014.

Comparison of Years Ended December 31, 2013 and 2012

Net loss attributable to common stockholders for the year ended December 31, 2013 was $56.1 million (or $1.60 per common share basic and diluted) compared with a net loss of $41.4 million (or $1.56 per common share basic and diluted) for the year ended December 31, 2012. The increase in our net loss in 2013 of $14.7 million was primarily due to a:

- $14.5 million increase in our research and development expenses that resulted primarily from the activities under our phase 3 clinical study in CF patients and related two-year, open-label safety study in Europe and Canada, and our phase 2 NTM clinical study in the United States. We initiated the phase 3 CF study and phase 2 NTM study in the second quarter of 2012 and initiated the two-year CF extension study in October 2012;
- $9.6 million increase in our general and administrative expenses that was due primarily to a $5.5 million increase in compensation expense (including an increase of $3.9 million in non-cash stock-based compensation expense), a $1.8 million increase in professional fees, including a $1.4 million increase in legal fees related to the investigation, accounting and reporting of excess equity awards and $2.9 million for consulting expenses, mainly for market research and other related costs;
- $1.7 million reduction in investment income and realized gains on investment due to lower interest rates and more conservative investments of cash balances; and
- $1.6 million increase in interest expense due to $20.0 million of borrowings ($10.0 million in June 2012 and $10.0 million in December 2012) under our Loan and Security Agreement we entered into in June 2012.

Partially offsetting these increases in operating expenses was other revenue of $11.5 million related to a one-time payment for the sale of the Company's right to receive future royalties under its license agreement with Premacure (now Shire plc). The net loss attributable to stockholders in 2013 and 2012 includes approximately $8.7 million and $3.0 million, respectively, in non-cash stock option compensation. The net loss attributable to stockholders in 2012 includes approximately $2.9 million in severance costs related to the termination of certain executives and employees.

Revenue

In 2013, our other revenue consisted solely of an $11.5 million payment received from Premacure (now Shire plc) in exchange for the Company's right to receive royalties under its license agreement with Premacure. We recorded this as other revenue after all four revenue recognition criteria were present and the Company had no continuing performance obligations related to the payment received. We did not recognize any revenue for the year ended December 31, 2012.

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Research and Development Expenses

Research and development expenses for the years ended December 31, 2013 and 2012, comprised the following:

	December 31,		Increase (Decrease)	
	2013	2012	$	%
External Expenses				
Clinical development	$ 19,728	$ 11,800	$ 7,928	67.2%
Manufacturing	7,906	7,254	652	9.0%
Regulatory and quality assuarance	2,010	2,315	(305)	-13.2%
Subtotal external expenses	$ 29,644	$ 21,369	$ 8,275	38.7%
Internal Expenses				
Compensation and related expenses	$ 10,327	$ 6,593	$ 3,734	56.6%
Other internal operating expenses	4,308	1,819	2,489	136.8%
Subtotal internal expenses	$ 14,635	$ 8,412	$ 6,223	74.0%
Total	$ 44,279	$ 29,781	$ 14,498	48.7%

Research and development expenses increased to $44.3 million in 2013 from $29.8 million in 2012. The $14.5 million increase is due primarily to:

- an $8.3 million increase in external costs primarily consisting of a $7.9 million increase in expenses for our phase 3 CF clinical study and our two-year, open-label safety study in Europe and Canada, and our phase 2 NTM clinical study in the US during year ended December 31, 2013. We initiated the phase 2 NTM study in the second quarter of 2012. We initiated the phase 3 CF study in the second quarter of 2012 and initiated the two-year CF extension study in October 2012; and
- a $6.2 million increase in internal expenses, including a $3.7 million increase in compensation and related expenses (including an increase of $1.7 million in non-cash stock-based compensation expense), a $0.8 million increase in recruiting expenses, a $0.3 million increase in travel expenses to clinical trial sites and manufacturing locations, and a $1.4 million increase in other research and development expenses.

General and Administrative Expenses

General and administrative expenses increased to $22.2 million in 2013 from $12.7 million in 2012. The $9.5 million increase was primarily due to:

- a $5.5 million increase in compensation expense (including an increase of $3.9 million in non-cash stock-based compensation expense);
- a $2.9 million increase in consulting expenses, mainly for market research and other related costs; and
- a $1.8 million increase in professional fees related primarily to a $1.4 million increase in legal fees resulting primarily from the investigation, accounting and reporting of excess equity awards

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(see Note 8, "Stock Based Compensation" to the consolidated financial statements for additional information).

The 2012 results included approximately $2.2 million in severance expenses related to the departure of several executives and employees.

Investment Income

Investment income decreased to $0.2 million in 2013 from $1.8 million in 2012. The $1.6 million decrease is a result of diminishing rates of return on our cash balances and more conservative investments of cash balances during 2013 compared to 2012.

Interest Expense

Interest expense increased to $2.4 million during 2013 compared to $0.8 million in 2012. The $1.6 million increase was due to $20.0 million of borrowings ($10.0 million in June 2012 and $10.0 million in December 2012) under our Loan and Security Agreement we entered into in June 2012.

LIQUIDITY AND CAPITAL RESOURCES

Overview

There is considerable time and cost associated with developing a potential drug or pharmaceutical product to the point of regulatory approval and commercialization. Historically, we have funded our operations through public and private placements of equity securities, through debt financing, from the proceeds from the sale of our follow-on biologics ("FOB") platform to Merck in 2009 and from revenues related to sales of product and our IPLEX expanded access program, which was discontinued in 2011. We expect to continue to incur losses because we plan to fund research and development activities and commercial launch activities, and we do not expect material revenues for at least the next two years.

We believe we currently have sufficient funds to meet our financial needs in 2015. We may opportunistically raise additional capital during the next twelve months and may do so through equity or debt financing(s), strategic transactions or otherwise. Such additional funding may be necessary to continue to develop our potential product candidates, to pursue the license or purchase of other technologies, to commercialize our product candidates or to purchase other products. We cannot assure you that adequate capital will be available on favorable terms, or at all, when needed. If we are unable to obtain sufficient additional funds when required, we may be forced to delay, restrict or eliminate all or a portion of our research or development programs, dispose of assets or technology or cease operations. During 2015 we plan to continue to fund further clinical development of ARIKAYCE and INS1009, invest in third-party manufacturing capacity, support efforts to obtain regulatory approvals and prepare for commercialization in certain European countries. Our cash requirements in 2015 will be impacted by a number of factors, the most significant of which, being the enrollment rates and other expenses related to the 212 study.

On August 18, 2014, we completed an underwritten public offering of 10,235,000 shares of our common stock, which included the underwriter's exercise in full of its over-allotment option of 1,335,000 shares, at a price to the public of $11.25 per share. Our net proceeds from the sale of the shares, after deducting the underwriter's discount and offering expenses of $7.1 million, were $108.0 million.

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Cash Flows

As of December 31, 2014, we had total cash and cash equivalents of $159.2 million, as compared with $113.9 million as of December 31, 2013. The $45.3 million net increase was due to our financing activities during 2014, which included $109.0 million of proceeds from the issuances of common stock, which were partially offset by the use of $64.4 million in operations. Our working capital was $145.1 million as of December 31, 2014.

Net cash used in operating activities was $64.4 million, $46.7 million, and $31.0 million for the years ended December 31, 2014, 2013 and 2012, respectively. Excluding (i) cash proceeds from the sale of a portion of our New Jersey State NOLs under the State of New Jersey's Technology Business Tax Certificate Transfer Program of $9.4 million and $1.2 million in 2014 and 2013, respectively, and (ii) the $11.5 million one-time payment from Premacure in the year ended December 31, 2013, net cash used in operating activities in 2014 and 2013 would have been $73.8 million and $59.4 million, respectively. The net cash used in operating activities during 2014, 2013 and 2012 was primarily for the clinical development of ARIKAYCE, which included the advancement of three clinical trials.

Net cash (used in) / provided by investing activities was $(5.4) million, $1.3 million, and $61.5 million for the years ended December 31, 2014, 2013 and 2012, respectively. The net cash used in investing activities in 2014 primarily related to our investment for the build out of our new headquarters and lab facility in Bridgewater, New Jersey. The net cash provided by investing activities in 2013 resulted from $2.2 million from the maturity of a certificate of deposit which was partially offset by fixed asset purchases of $0.8 million that were primarily for computers and lab equipment. The net cash provided by investing activities in 2012 was primarily a result of the net sales of short-term investments of $61.8 million.

Net cash provided by financing activities was $115.1 million, $68.4 million, and $45.4 million for the years ended December 31, 2014, 2013 and 2012, respectively. Net cash provided by financing activities in 2014 included $108.0 million of proceeds from the issuance of our common stock in an underwritten public offering in August 2014, $5.0 million of proceeds from the amendment of our loan agreement with Hercules in December 2014, $1.0 million of proceeds from the issuance of our common stock to Hercules in December 2014, and $1.4 million of proceeds received from stock option exercises. Net cash provided by financing activities in 2013 included $67.0 million of proceeds from the issuance of our common stock in an underwritten public offering in July 2013 and $1.6 million of proceeds received from stock option exercises. Net cash provided by financing activities in 2012 included $20.0 million of proceeds from the issuance of debt and $25.7 million of proceeds from the issuance of common stock registered in a direct public offering in September 2012.

Contractual Obligations

On June 29, 2012, we and our domestic subsidiaries, as co-borrowers, entered into a Loan and Security Agreement with Hercules that allowed us to borrow up $20.0 million in $10.0 million increments ("Loan Agreement"). We borrowed the first and second $10.0 million increments by signing two Secured Promissory Notes ("Note A" and "Note B" and collectively, the "Notes") on June 29, 2012 and December 27, 2012, respectively. Notes A and B bear interest at 9.25%. Note A was originally scheduled to be repaid over a 42-month period with the first twelve monthly payments representing interest only followed by thirty monthly equal payments of principal and interest. Note B was originally scheduled to be repaid over a 36-month period with the first six monthly payments representing interest only followed by thirty monthly equal payments of principal and interest. The Loan Agreement provided that in certain circumstances we could delay the first principal payment by five months. In July 2013, subsequent to the completion of certain ARIKAYCE-related development milestones, we

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elected to extend the interest only period under the Notes from July 31, 2013 to December 31, 2013 and delay the first monthly principal repayments for the Notes from August 1, 2013 to January 1, 2014. On November 25, 2013, we entered into an amendment (the "First Amendment") to the Loan Agreement with Hercules. The First Amendment initially extended the interest-only period through June 30, 2014 and called for the first monthly principal payment on July 1, 2014. The First Amendment also allowed us to further extend the interest-only period through December 31, 2014 and delay the first payment of principal until January 1, 2015, so long as we paid a $100,000 fee and obtained positive data from our phase 2 clinical trial of ARIKAYCE in patients who have lung infections caused by NTM. In June 2014, we paid the $100,000 fee and exercised our option to extend the interest-only period and delay the first payment of principal to January 1, 2015. The election and second amendment did not change the maturity date for Notes A and B, which is January 1, 2016. In connection with the Loan Agreement, we granted the lender a first position lien on all of our assets, excluding intellectual property. Prepayment of the loans made pursuant to the Loan Agreement is subject to penalty and we are required to pay an "end of term" charge of $390,000.

On December 15, 2014, we entered into a third amendment (the "Third Amendment") to the Loan and Security Agreement (the "Loan Agreement") with Hercules. In connection with the Third Amendment, we paid a commitment fee of $25,000, and at the closing, paid a facility fee of $125,000. Under the Third Amendment, the amount of borrowings was increased by $5.0 million to a total of $25.0 million and the interest-only period was extended through December 31, 2015. In addition, in the event we receive $90.0 million in cash proceeds from the completion of certain types of equity financings, subordinated debt financings, and/or up-front cash payments from corporate transactions prior to December 31, 2015, we will have the option to extend the maturity date of the loan to January 1, 2018. If we elect to exercise the option, we are required to pay Hercules a $250,000 fee. In connection with the Third Amendment, on December 15, 2014, we entered into a stock purchase agreement with Hercules pursuant to which we issued 70,771 shares of common stock, at a price of $14.13 per share (the closing price of our common stock on December 12, 2014), for an aggregate purchase price of approximately $1.0 million.

We have an operating lease for office and laboratory space located in Bridgewater, NJ that expires in November 2019. Future minimum rental payments under this lease total approximately $3.5 million. We continue to lease office space in Richmond, Virginia where our corporate headquarters was previously located. Future minimum rental payments under this lease total approximately $0.9 million. During 2011, we recorded a net present value charge of $1.2 million in general and administrative expenses associated with vacating the Richmond, Virginia facility. In December 2014, we entered into an agreement to sublet this space for the remainder of the lease term. We expect to collect proceeds from the sublease in the amount of $0.4 million over the remaining term of the lease.

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As of December 31, 2014, future payments under our long-term debt agreements, the capital leases and minimum future payments under non-cancellable operating leases are as follows:

	As of December 31, 2014 Payments Due By Period				
	Total	Less than 1 year	1 - 3 Years	4 - 5 Years	After 5 Years
	(In thousands)				
Debt obligations					
Debt maturities	$ 25,000	$ -	$ 25,000	$ -	$ -
Contractual interest	2,703	2,313	390	-	-
Capital lease obligations					
Debt maturities	-	-	-	-	-
Contractual interest	-	-	-	-	-
Operating leases	4,471	1,106	1,885	1,480	-
Purchase obligations	-	-	-	-	-
Total contractual obligations	$ 32,174	$ 3,419	$ 27,275	$ 1,480	$ -

This table does not include (a) any milestone payments which may become payable to third parties under our license and collaboration agreements as the timing and likelihood of such payments are not known, (b) any royalty payments to third parties as the amounts of such payments, timing and/or the likelihood of such payments are not known, (c) contracts that are entered into in the ordinary course of business which are not material in the aggregate in any period presented above or (d) any payments related to the agreements mentioned below.

We currently have a licensing agreement with PARI for use of the optimized eFlow Nebulizer System for delivery of ARIKAYCE in treating patients with NTM infections, CF and bronchiectasis. We have rights to several US and foreign issued patents, and patent applications involving improvements to the optimized eFlow Nebulizer System. Under the licensing agreement, PARI is entitled to receive payments either in cash, qualified stock or a combination of both, at PARI's discretion, based on achievement of certain milestone events including phase 3 trial initiation (which occurred in 2012), first acceptance of MAA submission (or equivalent) in the US of ARIKAYCE and the device, first receipt of marketing approval in the US for ARIKAYCE and the device, and first receipt of marketing approval in a major EU country for ARIKAYCE and the device. In addition, PARI is entitled to receive royalty payments on commercial sales of ARIKAYCE pursuant to the licensing agreement. In July 2014, we entered into a Commercialization Agreement (the "PARI Agreement") with PARI for the manufacture and supply of eFlow nebulizer systems and related accessories (the "Device") as optimized for use with our proprietary liposomal amikacin for inhalation. The PARI Agreement has an initial term of fifteen years from the first commercial sale of the Device (the "Initial Term"). The term of the PARI Agreement may be extended by us for an additional five years by providing written notice to PARI at the least one year prior to the expiration of the Initial Term.

In 2004 and 2009, we entered into a research funding agreements with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) whereby we received $1.7 million and $2.2 million for each respective agreement in research funding for the development of ARIKAYCE. If ARIKAYCE becomes an approved product for CF patients in the US, we will owe a payment to CFFT of up to $13.4 million that is payable over a three-year period after approval as a commercialized drug in the US. Furthermore, if certain global sales milestones are met within 5 years of the drug commercialization, we would owe an additional $3.9 million in additional payments. Since there is significant development risk associated with ARIKAYCE, we have not accrued these obligations.

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In 2009 and 2012, we entered into a cooperative research and development agreement (CRADA) with the National Institute of Allergy and Infectious Diseases (NIAID) to design and conduct our phase 2 study of ARIKAYCE in patients with NTM. NIAID has also agreed to provide biostatistical advisory input in connection with the phase 2 NTM study. If we decide not to continue with the commercialization of ARIKAYCE in NTM, NIAID will have the right to complete the clinical trial. Further NIAID may elect to pursue its rights to obtain license rights to certain inventions made under the CRADA.

In February 2014, we entered into a contract manufacturing agreement with Therapure for the manufacture of ARIKAYCE at the larger scales necessary to support commercialization. Pursuant to the agreement, we are collaborating with Therapure to construct a production area for the manufacture of ARIKAYCE in Therapure's existing manufacturing facility in Mississauga, Ontario, Canada. We expect to pay Therapure approximately $12 million for the build out of the construction area and related manufacturing costs, of which approximately $7 million has been paid as of December 31, 2014. Therapure will manufacture ARIKAYCE for us on a non-exclusive basis. The agreement has an initial term of five years from the first date on which Therapure delivers ARIKAYCE to us after we obtain permits related to the manufacture of ARIKAYCE.

In December 2014, we, entered into Work Order 1 (the "Work Order"), pursuant to a Master Agreement for Services ("MSA") with SynteractHCR, Inc., ("Synteract"), dated as of August 27, 2014, as amended on December 23, 2014, pursuant to which we retained Synteract to perform implementation and management services in connection with certain clinical trials pursuant to a specific protocol of pharmaceutical products under development by or under the control of the Company (each, a "Study"). Synteract is providing comprehensive services for Protocol INS-212, a randomized, open-label, multicenter study of liposomal amikacin for inhalation in adult patients with NTM lung infections caused by MAC complex that are refractory to treatment. Prior to the execution of the Work Order, Synteract was providing such services pursuant to a Letter of Intent, dated August 25, 2014. The Work Order covers services related to INS-212 only and any additional study or services will be subject to the negotiation and execution of an additional work order. It is anticipated that aggregate costs to us relating to this Work Order will be approximately $33 million over the period of the study.

Future Funding Requirements

We may need to raise additional capital to fund our operations, to develop and commercialize ARIKAYCE, to develop INS1009, and to develop, acquire, in-license or co-promote other products that address orphan or rare diseases. Our future capital requirements may be substantial and will depend on many factors, including:

- the timing and cost of our anticipated clinical trials of ARIKAYCE for the treatment of patients with NTM lung infections;
- the decisions of the FDA and EMA with respect to our applications for marketing approval of ARIKAYCE in the US and Europe; the costs of activities related to the regulatory approval process; and the timing of approvals, if received;
- the cost of putting in place the sales and marketing capabilities necessary to be prepared for a potential commercial launch of ARIKAYCE, if approved;
- the cost of filing, prosecuting and enforcing patent claims;
- the costs of our manufacturing-related activities;
- the costs associated with commercializing ARIKAYCE if we receive marketing approval; and
- subject to receipt of marketing approval, the levels, timing and collection of revenue received from sales of approved products, if any, in the future.

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In August 2014, we issued approximately $108.0 million worth of common stock. We believe we currently have sufficient funds to meet our financial needs for 2015. However, our business strategy may require us to, or we may otherwise determine to, raise additional capital at any time through equity or debt financing(s), strategic transactions or otherwise. Such additional funding may be necessary to continue to develop our potential product candidates, to pursue the license or purchase of complementary technologies, to commercialize our product candidates or to purchase other products. If we are unable to obtain additional financing, we may be required to reduce the scope of our planned product development and commercialization or our plans to establish a sales and marketing force, any of which could harm our business, financial condition and results of operations. The source, timing and availability of any future financing will depend principally upon equity and debt market conditions, interest rates and, more specifically, our continued progress in our regulatory, development and commercial activities. We cannot assure you that such capital funding will be available on favorable terms or at all. If we are unable to obtain sufficient additional funds when required, we may be forced to delay, restrict or eliminate all or a portion of our research or development programs, dispose of assets or technology or cease operations.

To date, we have not generated any revenue from ARIKAYCE. We do not know when or if we will generate any revenue. We do not expect to generate significant revenue unless or until we obtain marketing approval of, and commercialize, ARIKAYCE.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements, other than operating leases, that have or are reasonably likely to have a current or future material effect on our financial condition, revenues or expenses, results of operations, liquidity, capital expenditures or capital resources. We do not have any interest in special purpose entities, structured finance entities or other variable interest entities.

CRITICAL ACCOUNTING POLICIES

Preparation of financial statements in accordance with generally accepted accounting principles in the US requires us to make estimates and assumptions affecting the reported amounts of assets, liabilities, revenues and expenses and the disclosures of contingent assets and liabilities. We use our historical experience and other relevant factors when developing our estimates and assumptions. We continually evaluate these estimates and assumptions. The amounts of assets and liabilities reported in our consolidated balance sheets and the amounts of revenue reported in our consolidated statements of comprehensive loss are effected by estimates and assumptions, which are used for, but not limited to, the accounting for research and development, revenue recognition, beneficial conversion charge, stock-based compensation, identifiable intangible assets and goodwill, and accrued expenses. The accounting policies discussed below are considered critical to an understanding of our consolidated financial statements because their application places the most significant demands on our judgment. Actual results could differ from our estimates. For additional accounting policies, see Note 2 to our Consolidated Financial Statements "Summary of Significant Accounting Policies."

Research and Development

Research and development expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving our research and development functions, and other internal operating expenses, the cost of manufacturing our drug candidate for clinical study, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. Our expenses related to manufacturing our drug candidate for clinical study are primarily related to activities at contract manufacturing organizations that manufacture ARIKAYCE for our use.

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Our expenses related to clinical trials are primarily related to activities at contract research organizations that conduct and manage clinical trials on our behalf. These contracts set forth the scope of work to be completed at a fixed fee or amount per patient enrolled. Payments under these contracts depend on performance criteria such as the successful enrollment of patients or the completion of clinical trial milestones as well as time-based fees. Expenses are accrued based on contracted amounts applied to the level of patient enrollment and to activity according to the clinical trial protocol.

Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized. Such amounts are then recognized as an expense as the related goods are delivered or the services are performed, or when the goods or services are no longer expected to be provided.

Revenue Recognition

In the periods when we record revenue, we recognize revenues when all of the following four criteria are present: persuasive evidence of an arrangement exists; delivery has occurred or services have been rendered; the fee is fixed or determinable; and collectability is reasonably assured. We did not record any revenue for the years ended December 31, 2014 and 2012.

Where we have continuing performance obligations under the terms of a collaborative arrangement, non-refundable upfront license payments received upon contract signing are recorded as deferred revenue and recognized as revenue as the related activities are performed. The period over which these activities are to be performed is based upon management's estimate of the development period. Changes in management's estimate could change the period over which revenue is recognized. Research and/or development payments are recognized as revenues as the related research and/or development activities are performed and when we have no continuing performance obligations related to the research and development payment received.

Where we have no continuing involvement under a collaborative arrangement, we record nonrefundable license fee revenues when we have the contractual right to receive the payment, in accordance with the terms of the collaboration agreement, and record milestones upon appropriate notification to us of achievement of the milestones by the collaborative partner.

We recognize revenue from milestone payments when earned, provided that (i) the milestone event is substantive and its achievability was not reasonably assured at the inception of the agreement and (ii) we do not have ongoing performance obligations related to the achievement of the milestone earned. Milestone payments are considered substantive if all of the following conditions are met: the milestone payment (a) is commensurate with either the vendor's performance to achieve the milestone or the enhancement of the value of the delivered item or items as a result of a specific outcome resulting from the vendor's performance to achieve the milestone, (b) relates solely to past performance, and (c) is reasonable relative to all of the deliverables and payment terms (including other potential milestone consideration) within the arrangement. Any amounts received under the agreement in advance of performance, if deemed substantive, are recorded as deferred revenue and recognized as revenue as we complete our performance obligations.

With regard to recognizing revenue for multiple deliverable revenue arrangements, each deliverable within a multiple-deliverable revenue arrangement is accounted for as a separate unit of accounting if both of the following criteria are met: (1) the delivered item or items have value to the customer on a standalone basis and (2) for an arrangement that includes a general right of return relative to the delivered item(s), delivery or performance of the undelivered item(s) is considered probable and substantially in our control.

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In addition, multiple deliverable revenue arrangement consideration is allocated at the inception of an arrangement to all deliverables using the relative selling price method. We also apply a selling price hierarchy for determining the selling price of a deliverable, which includes (1) vendor-specific objective evidence, if available, (2) third-party evidence, if vendor-specific objective evidence is not available, and (3) estimated selling price if neither vendor-specific nor third-party evidence is available.

Deferred revenue associated with a non-refundable payment received under a collaborative agreement that is terminated prior to its completion results in an immediate recognition of the deferred revenue.

Stock-Based Compensation

We recognize stock-based compensation expense for awards of equity instruments to employees and directors based on the grant-date fair value of those awards. The grant-date fair value of the award is recognized as compensation expense ratably over the requisite service period, which generally equals the vesting period of the award, and if applicable, is adjusted for expected forfeitures. We also grant performance-based stock options to employees. The grant-date fair value of the performance-based stock options is recognized as compensation expense over the implicit service period using the accelerated attribution method once it is probable that the performance condition will be achieved. Stock-based compensation expense is included in both research and development expenses and general and administrative expenses in the Consolidated Statements of Comprehensive Loss. For awards that were deemed to be granted outside of the Company's 2000 Stock Incentive Plan, we used liability accounting. These awards were classified as a liability and were remeasured at fair value at the end of each reporting period. Changes in fair value are included in compensation expense in the Consolidated Statements of Comprehensive Loss (see additional disclosures related to awards granted outside of the 2000 Stock Incentive Plan in Footnote 8 "Stock-Based Compensation" of our consolidated financial statements located in Part IV, Item 15 of this Annual Report on Form 10-K).

The following table summarizes the assumptions used in determining the fair value of stock options granted during the years ended December 31, 2014, 2013 and 2012:

	2014	2013	2012
Volatility	83% - 86%	86% - 96%	99% - 107%
Risk-free interest rate	1.46% - 1.83%	0.65% - 1.65%	0.57% - 0.99%
Dividend yield	0.0%	0.0%	0.0%
Expected option term (in years)	6.25	6.25	6.25

For the years ended December 31, 2014, 2013 and 2012, the volatility factor was based on our historical volatility since the closing of our merger with Transave, Inc. on December 1, 2010. The expected life was determined using the simplified method as described in ASC Topic 718, "Accounting for Stock Compensation", which is the midpoint between the vesting date and the end of the contractual term. The risk-free interest rate is based on the US Treasury yield in effect at the date of grant. Forfeitures are based on actual percentage of option forfeitures since the closing of the merger on December 1, 2010 and are the basis for future forfeiture expectations.

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Identifiable Intangible Assets

Identifiable intangible assets are measured at their respective fair values and are not amortized until commercialization. Once commercialization occurs, these intangible assets will be amortized over their estimated useful lives. The fair values assigned to our intangible assets are based on reasonable estimates and assumptions given available facts and circumstances. Unanticipated events or circumstances may occur that may require us to review the assets for impairment. Events or circumstances that may require an impairment assessment include negative clinical trial results, the non-approval of a new drug application by a regulatory agency, material delays in our development program or a sustained decline in market capitalization.

Indefinite-lived intangible assets are not subject to periodic amortization. Rather, indefinite-lived intangibles are reviewed for impairment by applying a fair value based test on an annual basis or more frequently if events or circumstances indicate impairment may have occurred. Events or circumstances that may require an interim impairment assessment are consistent with those described above. We perform our annual impairment test as of October 1 of each year.

We use the income approach to derive the fair value of in-process research and development assets. This approach calculates fair value by estimating future cash flows attributable to the assets and then discounting these cash flows to a present value using a risk-adjusted discount rate. A market based valuation approach was not considered given a lack of revenues and profits by us. This approach requires significant management judgment with respect to unobservable inputs such as future volume, revenue and expense growth rates, changes in working capital use, appropriate discount rates and other assumptions and estimates. The estimates and assumptions used are consistent with our business plans.

Accrued Expenses

We are required to estimate accrued expenses as part of our process of preparing financial statements. This process involves estimating the level of service performed on our behalf and the associated cost incurred in instances where we have not been invoiced or otherwise notified of actual costs. Examples of areas in which subjective judgments may be required include costs associated with services provided by contract organizations for preclinical development, clinical trials and manufacturing of clinical materials. We accrue for expenses associated with these external services by determining the total cost of a given study based on the terms of the related contract. We accrue for costs incurred as the services are being provided by monitoring the status of the trials and the invoices received from our external service providers. In the case of clinical trials, the estimated cost normally relates to the projected costs of having subjects enrolled in our trials, which we recognize over the estimated term of the trial according to the number of subjects enrolled in the trial on an ongoing basis, beginning with subject enrollment. As actual costs become known to us, we adjust our accruals. To date, the number of clinical trials and related research service agreements has been relatively limited and our estimates have not differed significantly from the actual costs incurred.

New Accounting Pronouncements

In May 2014, the FASB issued Accounting Standards Update No. 2014-09, *Revenue from Contracts with Customers (Topic 606)*, ("ASU 2014-09"). ASU 2014-09 outlines a new, single comprehensive model for entities to use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance, including industry-specific guidance. This new revenue recognition model provides a five-step analysis in determining when and how revenue is recognized. The new model will require revenue recognition to depict the transfer of promised goods or services to customers in an amount that reflects the consideration a company

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expects to receive in exchange for those goods or services. ASU 2014-09 is effective for public entities for annual reporting periods beginning after December 15, 2016 and interim periods within those periods. Early adoption is not permitted. Companies may use either a full retrospective or a modified retrospective approach to adopt ASU 2014-09. We are currently evaluating the impact this standard will have on our operating results in future periods when revenue is recorded.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As of December 31, 2014, our cash and cash equivalents were in cash accounts or were invested in money funds. Such accounts or investments are not insured by the federal government.

As of December 31, 2014, we had $25.0 million of fixed rate borrowings bearing interest at 9.25% outstanding under a Loan and Security Agreement we entered into in June 2012 and amended most recently in December 2014. If a 10% change in interest rates were to have occurred on December 31, 2014, this change would not have had a material effect on the fair value of our debt as of that date, nor would it have had a material effect on our future earnings or cash flows.

The majority of our business is conducted in US dollars. However, we do conduct certain transactions in other currencies, including Euros and British Pounds. Fluctuations in foreign currency exchange rates do not materially affect our results of operations. During 2014, 2013 and 2012, our results of operations were not materially affected by fluctuations in foreign currency exchange rates.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The information required by Item 8 is included in our Financial Statements and Supplementary Data listed in Item 15 of Part IV of this Annual Report on Form 10-K.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2014. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures that are designed to provide reasonable assurance that information required to be disclosed by us in the periodic reports that we file or submit with the SEC is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms, and to ensure that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate to allow timely decisions regarding required disclosure. Based on that evaluation as of December 31, 2014 our Chief Executive Officer and Chief Financial Officer have concluded that our disclosure controls and procedures are effective at the reasonable assurance level.

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Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) and 15d-15(f) under the Securities Exchange Act of 1934, as amended, as a process designed by, or under the supervision of, our principal executive and principal financial and accounting officers and effected by our board of directors and management to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. generally accepted accounting principles, and that receipts and expenditures of our company are being made only in accordance with authorizations of our management and board of directors; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risks that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2014, based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control Integrated Framework (2013 framework). A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of a company's annual or interim financial statements will not be prevented or detected on a timely basis. Based on management's assessment, management concluded that the Company's internal control over financial reporting was effective as of December 31, 2014.

Ernst & Young LLP, our independent registered public accounting firm, issued an attestation report on our internal control over financial reporting. The report of Ernst & Young LLP is contained in Item 15 of Part IV of this Annual Report on Form 10-K.

ITEM 9B. OTHER INFORMATION

None

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PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

Pursuant to General Instruction G(3) of Form 10-K, the information required by Item 10 of Form 10-K is hereby incorporated by reference from the discussion responsive thereto under the captions "Election of Directors," "Corporate Governance" and "Section 16(a) Beneficial Ownership Reporting Compliance" in our definitive proxy statement for our 2015 annual meeting of stockholders to be filed with the SEC.

ITEM 11. EXECUTIVE COMPENSATION

Pursuant to General Instruction G(3) of Form 10-K, the information required by Item 11 of Form 10-K is hereby incorporated by reference from the discussion responsive thereto under the captions "Compensation Discussion and Analysis," "Compensation Committee Report," "Compensation Committee Interlocks and Insider Participation" and "Directors Compensation" in our definitive proxy statement for our 2015 annual meeting of stockholders to be filed with the SEC.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

Pursuant to General Instruction G(3) of Form 10-K, the information required by Item 12 of Form 10-K is hereby incorporated by reference from the discussion responsive thereto under the captions "Compensation Discussion and Analysis," "Security Ownership of Certain Beneficial Owners" and "Security Ownership of Directors and Management" in our definitive proxy statement for our 2015 annual meeting of stockholders to be filed with the SEC.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS AND DIRECTOR INDEPENDENCE

Pursuant to General Instruction G(3) of Form 10-K, the information required by Item 13 of Form 10-K is hereby incorporated by reference from the discussion responsive thereto under the captions "Election of Directors" and "Certain Relationships and Related Transactions" in our definitive proxy statement for our 2015 annual meeting of stockholders to be filed with the SEC.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

Pursuant to General Instruction G(3) of Form 10-K, the information required by Item 14 of Form 10-K is hereby incorporated by reference from the discussion responsive thereto under the caption "Corporate Governance" and "Ratification of Independent Public Accountants" in our definitive proxy statement for our 2015 annual meeting of stockholders to be filed with the SEC.

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PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a)

Documents filed as part of this report.

1.

FINANCIAL STATEMENTS. The following consolidated financial statements of the Company are set forth herein, beginning on page 103:

(i) Reports of Independent Registered Public Accounting Firm

(ii) Consolidated Balance Sheets as of December 31, 2014 and 2013

(iii) Consolidated Statements of Comprehensive Loss for the Years Ended December 31, 2014, 2013 and 2012

(iv) Consolidated Statements of Stockholders' Equity for the Years Ended December 31, 2014, 2013 and 2012

(v) Consolidated Statements of Cash Flows for the Years Ended December 31, 2014, 2013 and 2012

(vi) Notes to Consolidated Financial Statements

2.

FINANCIAL STATEMENT SCHEDULES.

None required.

3.

EXHIBITS.

The exhibits that are required to be filed or incorporated by reference herein are listed in the Exhibit Index.

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized on February 27, 2015.

INSMED INCORPORATED
a Virginia corporation
(Registrant)

By: /s/ WILLIAM H. LEWIS

William H. Lewis
President and Chief Executive Officer (Principal Executive Officer) and Director

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities indicated on February 27, 2015.

Signature	Title
/s/ WILLIAM H. LEWIS William H. Lewis	President and Chief Executive Officer (Principal Executive Officer) and Director
/s/ ANDREW T. DRECHSLER Andrew T. Drechsler	Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)
/s/ DONALD HAYDEN, JR. Donald Hayden, Jr.	Chairman of the Board of Directors
/s/ ALFRED F. ALTOMARI Alfred F. Altomari	Director
/s/ DAVID R. BRENNAN David R. Brennan	Director
/s/ STEINAR J. ENGELSEN, M.D. Steinar J. Engelsen, M.D.	Director
/s/ DAVID W.J. MCGIRR David W.J. McGirr	Director
/s/ MYRTLE POTTER Myrtle Potter	Director

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Signature	Title
/s/ MELVIN SHAROKY, M.D. Melvin Sharoky, M.D.	Director
/s/ RANDALL W. WHITCOMB, M.D. Randall W. Whitcomb, M.D.	Director

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Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of Insmed Incorporated

We have audited the accompanying consolidated balance sheets of Insmed Incorporated as of December 31, 2014 and 2013, and the related consolidated statements of comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2014. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Insmed Incorporated at December 31, 2014 and 2013, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2014, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), Insmed Incorporated's internal control over financial reporting as of December 31, 2014, based on criteria established in Internal Control Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 27, 2015 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

MetroPark, New Jersey
February 27, 2015

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Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of Insmed Incorporated

We have audited Insmed Incorporated's internal control over financial reporting as of December 31, 2014, based on criteria established in Internal Control Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). Insmed Incorporated's management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion, Insmed Incorporated maintained, in all material respects, effective internal control over financial reporting as of December 31, 2014, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of Insmed Incorporated as of December 31, 2014 and 2013, and the related consolidated statements of comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2014 and our report dated February 27, 2015 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

MetroPark, New Jersey
February 27, 2015

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INSMED INCORPORATED
Consolidated Balance Sheets
(in thousands, except par value and share data)

	As of December 31,	
	2014	**2013**
Assets		
Current assets:		
Cash and cash equivalents	$ 159,226	$ 113,894
Prepaid expenses and other current assets	5,488	2,269
Total current assets	164,714	116,163
In-process research and development	58,200	58,200
Fixed assets, net	7,534	1,812
Other assets	416	323
Total assets	$ 230,864	$ 176,498
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 9,249	$ 5,929
Accrued expenses	5,321	3,905
Accrued compensation	4,317	2,839
Accrued lease expense, current	320	307
Deferred rent	423	129
Capital lease obligations, current	-	64
Current portion of long-term debt	-	3,283
Total current liabilities	19,630	16,456
Long-term liabilities:		
Accrued lease expense, long-term	118	380
Other long-term liabilities	23	-
Debt, long-term	24,856	16,338
Total liabilities	44,627	33,174
Shareholders' equity:		
Common stock, $0.01 par value; 500,000,000 authorized shares, 49,806,131 and 39,137,169 issued and outstanding shares at December 31, 2014 and December 31, 2013, respectively	498	391
Additional paid-in capital	656,519	534,554
Accumulated deficit	(470,780)	(391,621)
Total shareholders' equity	186,237	143,324
Total liabilities and shareholders' equity	$ 230,864	$ 176,498

See accompanying notes to consolidated financial statements

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INSMED INCORPORATED
Consolidated Statements of Comprehensive Loss
(in thousands, except per share data)

	Years ended December 31,		
	2014	**2013**	**2012**
Other revenue	$ -	$ 11,500	$ -
Total revenues	-	11,500	-
Operating expenses:			
Research and development	56,292	44,279	29,781
General and administrative	31,073	22,236	12,657
Total operating expenses	87,365	66,515	42,438
Operating loss	(87,365)	(55,015)	(42,438)
Investment income	58	166	1,822
Interest expense	(2,415)	(2,412)	(763)
Other income/(expense), net	141	(33)	5
Loss before income taxes	(89,581)	(57,294)	(41,374)
Benefit from income taxes	(10,422)	(1,221)	-
Net loss	$ (79,159)	$ (56,073)	$ (41,374)
Basic and diluted net loss per share	$ (1.84)	$ (1.60)	$ (1.56)
Weighted average basic and diluted common shares outstanding	43,095	34,980	26,545
Net loss	$ (79,159)	$ (56,073)	$ (41,374)
Comprehensive loss:			
Unrealized loss on investments, net of taxes	-	-	(450)
Comprehensive loss	$ (79,159)	$ (56,073)	$ (41,824)

See accompanying notes to audited consolidated financial statements

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INSMED INCORPORATED
Consolidated Statements of Stockholders' Equity
(in thousands)

	Common Stock		Warrant		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total
	Shares	Amount	Shares	Amount				
Balance at December 31, 2011	24,833	$ 248	-	$ -	$ 427,743	$ (294,174)	$ 450	$ 134,267
Comprehensive loss:								
Net loss						(41,374)		(41,374)
Unrealized loss on investments, net							(450)	(450)
Exercise of stock options	30	1			213			214
Net proceeds from issuance of common stock	6,304	63			25,595			25,658
Issuance of common stock for vesting of RSUs	321	3			(3)			-
Fair value of warrants granted in connection with debt financing			330	790				790
Stock compensation expense					1,777			1,777
Balance at December 31, 2012	31,488	$ 315	330	$ 790	$ 455,325	$ (335,548)	$ -	$ 120,882
Comprehensive loss:								
Net loss						(56,073)		(56,073)
Exercise of stock options	372	4			1,622			1,626
Net proceeds from issuance of common stock	6,900	69			66,948			67,017
Issuance of common stock for vesting of RSUs	154	1			(1)			-
Exercise of warrants	223	2	(330)	(790)	788			-
Reclass of stock compensation expense for liability awards to equity					3,371			3,371
Stock compensation expense					6,501			6,501
Balance at December 31, 2013	39,137	$ 391	-	$ -	$ 534,554	$ (391,621)	$ -	$ 143,324
Comprehensive loss:								
Net loss						(79,159)		(79,159)
Exercise of stock options	283	3			1,728			1,731
Net proceeds from issuance of common stock	10,306	103			108,910			109,013
Issuance of common stock for vesting of RSUs	80	1			(1)			-
Stock compensation expense					11,328			11,328
Balance at December 31, 2014	49,806	$ 498	-	$ -	$ 656,519	$ (470,780)	$ -	$ 186,237

See accompanying notes to audited consolidated financial statements

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INSMED INCORPORATED
Consolidated Statements of Cash Flows
(in thousands)

	Years ended December 31,		
	2014	**2013**	**2012**
Operating activities			
Net loss	$ (79,159)	$ (56,073)	$ (41,374)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	1,073	680	561
Stock based compensation expense	11,328	8,668	2,981
Loss / (gain) on sale of assets, net	9	(2)	(5)
Gain on sale of short-term investments, net	-	-	(833)
Amortization of debt discount and debt issuance costs	390	333	236
Accrual of the end of term charge on the debt	110	160	44
Changes in operating assets and liabilities:			
Accounts receivable	-	-	757
Prepaid expenses and other assets	(2,972)	(1,832)	(180)
Accounts payable	3,312	(1,131)	4,726
Accrued expenses, deferred rent and other	264	2,156	922
Accrued lease expenses	(249)	(255)	(259)
Accrued compensation	1,478	632	1,412
Net cash used in operating activities	(64,416)	(46,664)	(31,012)
Investing activities			
Purchase of fixed assets	(5,351)	(826)	(290)
Proceeds from sale of asset	10	2	5
Maturity of a certificate of deposit	-	2,153	-
Sales of short-term investments	-	-	81,464
Purchases of short-term investments	-	-	(19,657)
Net cash (used in) / provided by investing activities	(5,341)	1,329	61,522
Financing activities			
Payments on capital lease obligations	(64)	(96)	(120)
Proceeds from issuance of debt	5,000	-	20,000
Proceeds from issuance of common stock	109,013	67,017	25,658
Proceeds from exercise of stock options	1,390	1,626	214
Payment of debt issuance costs	(250)	(100)	(328)
Net cash provided by financing activities	115,089	68,447	45,424
Increase in cash and cash equivalents	45,332	23,112	75,934
Cash and cash equivalents at beginning of period	113,894	90,782	14,848
Cash and cash equivalents at end of period	$ 159,226	$ 113,894	$ 90,782
Supplemental disclosures of cash flow information:			
Cash paid for interest	$ 1,803	$ 1,809	$ 398

Cash received for taxes, net	$ 9,429	$ 1,221	$ -
Supplemental disclosures of non-cash investing and financing activities:			
Unrealized loss on investments	$ -	$ -	$ (450)
Value of warrant exercised by converting the warrant into shares of common stock ("net issuance method")	$ -	$ 790	$ -
Fair value of warrant granted in connection with debt financing	$ -	$ -	$ 790

See accompanying notes to audited consolidated financial statements

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Description of Business and Basis of Presentation

Description of Business Insmed is a biopharmaceutical company dedicated to improving the lives of patients battling serious lung diseases. The Company is focused on the development and commercialization of ARIKAYCE, or liposomal amikacin for inhalation, for at least two identified orphan patient populations: patients with nontuberculous mycobacteria (NTM) lung infections and cystic fibrosis (CF) patients with Pseudomonas aeruginosa lung infections. The Company is also focused on the development of INS1009, an inhaled treprostinil prodrug. Treprostinil is a prostacyclin used in the treatment of pulmonary arterial hypertension (PAH), a chronic, life-threatening disorder characterized by abnormally high blood pressure in the arteries between the heart and lungs.

The Company was incorporated in the Commonwealth of Virginia on November 29, 1999. On December 1, 2010, the Company completed a business combination with Transave, Inc. (Transave), a privately held, New Jersey-based pharmaceutical company focused on the development of differentiated and innovative inhaled pharmaceuticals for the treatment of serious lung infections. The Company's continuing operations are based on the technology and products historically developed by Transave. The Company's principal executive offices are located in Bridgewater, New Jersey.

Basis of Presentation The consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries, Transave, LLC, Insmed Pharmaceuticals, Incorporated, Insmed Limited, Celtrix Pharmaceuticals, Incorporated (Celtrix), Insmed Holdings Limited and Insmed Ireland Limited. All significant intercompany balances and transactions have been eliminated in consolidation.

2. Summary of Significant Accounting Policies

Use of Estimates The preparation of the consolidated financial statements in conformity with accounting principles generally accepted in the United States (GAAP) requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. The Company bases its estimates and judgments on historical experience and on various other assumptions. The amounts of assets and liabilities reported in the Company's balance sheets and the amounts of expenses reported for each period presented are effected by estimates and assumptions, which are used for, but not limited to, the accounting for stock-based compensation, income taxes, loss contingencies, and accounting for research and development costs. Actual results could differ from those estimates.

Investment Income and Interest Expense Investment income consists of interest and dividend income earned on the Company's cash, cash equivalents and short-term investments, along with realized gains (losses) on the sale of investments. Interest expense consists primarily of interest costs related to the Company's debt.

Cash and Cash Equivalents The Company considers cash equivalents to be highly liquid investments with maturities of three months or less from the date of purchase.

Fixed Assets, Net Fixed assets are recorded at cost and are depreciated on a straight-line basis over the estimated useful lives of the assets. Estimated useful lives of three to five years are used for computer equipment. Estimated useful lives of seven years are used for laboratory equipment, office equipment and furniture and fixtures. Leasehold improvements are amortized over the shorter of the

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

lease term or the estimated useful life of the asset. Long-lived assets are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to estimated undiscounted future cash flows expected to be generated by the asset. If the carrying amount of an asset exceeds its estimated future cash flows, then an impairment charge is recognized for the amount by which the carrying value of the asset exceeds the fair value of the asset.

Identifiable Intangible Assets Identifiable intangible assets are measured at their respective fair values and are not amortized until commercialization. Once commercialization occurs, these intangible assets will be amortized over their estimated useful lives. The fair values assigned to the Company's intangible assets are based on reasonable estimates and assumptions given available facts and circumstances. Unanticipated events or circumstances may occur that may require the Company to review the assets for impairment. Events or circumstances that may require an impairment assessment include negative clinical trial results, the non-approval of a new drug application by a regulatory agency, material delays in the Company's development program or a sustained decline in market capitalization.

Indefinite-lived intangible assets are not subject to periodic amortization. Rather, indefinite-lived intangibles are reviewed for impairment by applying a fair value based test on an annual basis or more frequently if events or circumstances indicate impairment may have occurred. Events or circumstances that may require an interim impairment assessment are consistent with those described above. The Company performs its annual impairment test as of October 1 of each year.

The Company uses the income approach to derive the fair value of in-process research and development assets. This approach calculates fair value by estimating future cash flows attributable to the assets and then discounting these cash flows to a present value using a risk-adjusted discount rate. A market based valuation approach was not considered given a lack of revenues and profits for the Company. This approach requires significant management judgment with respect to unobservable inputs such as future volume, revenue and expense growth rates, changes in working capital use, appropriate discount rates and other assumptions and estimates. The estimates and assumptions used are consistent with the Company's business plans.

Debt Issuance Costs Debt issuance costs are amortized using the effective interest rate method and amortized to interest expense over the term of the debt. Debt issuance costs paid to the lender are reflected as a discount to the debt, and debt issuance costs paid to other third parties are reflected as other assets in the consolidated balance sheets.

Fair Value Measurements The Company categorizes its financial assets and liabilities measured and reported at fair value in the financial statements on a recurring basis based upon the level of judgments associated with the inputs used to measure their fair value. Hierarchical levels, which are directly related to the amount of subjectivity associated with the inputs used to determine the fair value of financial assets and liabilities, are as follows:

- Level 1 Inputs are unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

- Level 2 Inputs (other than quoted prices included in Level 1) are either directly or indirectly observable for the assets or liability through correlation with market data at the measurement date and for the duration of the instrument's anticipated life.
- Level 3 Inputs reflect management's best estimate of what market participants would use in pricing the asset or liability at the measurement date. Consideration is given to the risk inherent in the valuation technique and the risk inherent in the inputs to the model.

Each major category of financial assets and liabilities measured at fair value on a recurring basis are categorized based upon the lowest level of significant input to the valuations. The fair value hierarchy also requires an entity to maximize the use of observable inputs and minimize the use of unobservable inputs when measuring fair value. Financial instruments in Level 1 generally include US treasuries and mutual funds listed in active markets.

The Company's only assets and liabilities which were measured at fair value as of December 31, 2014 and December 31, 2013 were its cash and cash equivalents of $159.2 million and $113.9 million, respectively. These amounts were measured at Level 1 using quoted prices in active markets for identical assets at the measurement date. The Company's cash and cash equivalents permit daily redemption and the fair values of these investments are based upon the quoted prices in active markets provided by the holding financial institutions. Cash equivalents consist of liquid investments with a maturity of three months or less from the date of purchase and the short-term investments consist of instruments with maturities greater than three months.

The Company recognizes transfers between levels within the fair value hierarchy, if any, at the end of each quarter. There were no transfers in or out of Level 1, Level 2 or Level 3 during 2014 and 2013.

As of December 31, 2014 and 2013, the Company held no securities that were in an unrealized loss or gain position. The Company's unrealized loss on investments for the year ended 2012 was $0.5 million, which was included in other comprehensive loss. During 2012, the Company realized a net gain of $0.8 million from the sale of short term investments.

The Company reviews the status of each security quarterly to determine whether an other-than-temporary impairment has occurred. In making its determination, the Company considers a number of factors, including: (1) the significance of the decline, (2) whether the securities were rated below investment grade, (3) how long the securities have been in an unrealized loss position, and (4) the Company's ability and intent to retain the investment for a sufficient period of time for it to recover.

Concentration of Credit Risk Financial instruments that potentially subject the Company to concentrations of credit risk consist primarily of cash and cash equivalents. The Company places its cash equivalents with high credit-quality financial institutions and may invest its short-term investments in US treasury securities, mutual funds and government agency bonds. The Company has established guidelines relative to credit ratings and maturities that seek to maintain safety and liquidity.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

The Company sources its raw materials from single suppliers. In addition, the production of the Company's lead product candidate, ARIKAYCE, is currently performed by a sole manufacturer. In February 2014, the Company entered into a contract manufacturing agreement with a second manufacturer to construct a production area and eventually supply ARIKAYCE at the larger scales necessary to support commercialization. The inability of the suppliers or manufacturers to fulfill supply requirements of the Company could materially impact future operating results. A change in the relationship with the suppliers or manufacturer, or an adverse change in their business, could materially impact future operating results.

Revenue Recognition The Company did not recognize any revenue in 2014 and 2012. In 2013, the Company's other revenue solely consists of an $11.5 million payment received from Premacure (now Shire plc) in exchange for the Company's right to receive royalties under its license agreement with Premacure. The Company recorded this as other revenue after all four revenue recognition criteria were present and the Company had no continuing performance obligations related to the payment received.

The Company recognizes revenues when all of the following four criteria are present: persuasive evidence of an arrangement exists; delivery has occurred or services have been rendered; the fee is fixed or determinable; and collectability is reasonably assured.

Where the Company has continuing performance obligations under the terms of a collaborative arrangement, non-refundable upfront license payments received upon contract signing are recorded as deferred revenue and recognized as revenue as the related activities are performed. The period over which these activities are to be performed is based upon management's estimate of the development period. Changes in management's estimate could change the period over which revenue is recognized. Research and/or development payments are recognized as revenues as the related research and/or development activities are performed and when the Company has no continuing performance obligations related to the research and development payment received.

Where the Company has no continuing involvement under a collaborative arrangement, the Company records nonrefundable license fee revenues when the Company has the contractual right to receive the payment, in accordance with the terms of the collaboration agreement, and records milestones upon appropriate notification to the Company of achievement of the milestones by the collaborative partner.

The Company recognizes revenue from milestone payments when earned, provided that (i) the milestone event is substantive and its achievability was not reasonably assured at the inception of the agreement and (ii) the Company does not have ongoing performance obligations related to the achievement of the milestone earned. Milestone payments are considered substantive if all of the following conditions are met: the milestone payment (a) is commensurate with either the vendor's performance to achieve the milestone or the enhancement of the value of the delivered item or items as a result of a specific outcome resulting from the vendor's performance to achieve the milestone, (b) relates solely to past performance, and (c) is reasonable relative to all of the deliverables and payment terms (including other potential milestone consideration) within the arrangement. Any

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

amounts received under the agreement in advance of performance, if deemed substantive, are recorded as deferred revenue and recognized as revenue as the Company completes its performance obligations.

With regard to recognizing revenue for multiple deliverable revenue arrangements, each deliverable within a multiple-deliverable revenue arrangement is accounted for as a separate unit of accounting if both of the following criteria are met: (1) the delivered item or items have value to the customer on a standalone basis and (2) for an arrangement that includes a general right of return relative to the delivered item(s), delivery or performance of the undelivered item(s) is considered probable and substantially in the Company's control.

In addition, multiple deliverable revenue arrangement consideration is allocated at the inception of an arrangement to all deliverables using the relative selling price method. The Company also applies a selling price hierarchy for determining the selling price of a deliverable, which includes (1) vendor-specific objective evidence, if available, (2) third-party evidence, if vendor-specific objective evidence is not available, and (3) estimated selling price if neither vendor-specific nor third-party evidence is available.

Deferred revenue associated with a non-refundable payment received under a collaborative agreement that is terminated prior to its completion results in an immediate recognition of the deferred revenue.

Research and Development Research and development expenses consist primarily of salaries, benefits and other related costs, including stock based compensation, for personnel serving in the Company's research and development functions, and other internal operating expenses, the cost of manufacturing a drug candidate, including the medical devices for drug delivery, for clinical study, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. The Company's expenses related to manufacturing its drug candidate and medical devices for clinical study are primarily related to activities at contract manufacturing organizations that manufacture ARIKAYCE and the medical devices for the Company's use. The Company's expenses related to clinical trials are primarily related to activities at contract research organizations that conduct and manage clinical trials on the Company's behalf. These contracts set forth the scope of work to be completed at a fixed fee or amount per patient enrolled. Payments under these contracts primarily depend on performance criteria such as the successful enrollment of patients or the completion of clinical trial milestones as well as time-based fees. Expenses are accrued based on contracted amounts applied to the level of patient enrollment and to activity according to the clinical trial protocol. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized. Such amounts are then recognized as an expense as the related goods are delivered or the services are performed, or when the goods or services are no longer expected to be provided.

Stock-Based Compensation The Company recognizes stock-based compensation expense for awards of equity instruments to employees and directors based on the grant-date fair value of those awards. The grant-date fair value of the award is recognized as compensation expense ratably over the requisite service period, which generally equals the vesting period of the award, and if applicable, is adjusted for expected forfeitures. The Company also grants performance-based stock options to

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

employees. The grant-date fair value of the performance-based stock options is recognized as compensation expense over the implicit service period using the accelerated attribution method once it is probable that the performance condition will be achieved. Stock-based compensation expense is included in both research and development expenses and general and administrative expenses in the Consolidated Statements of Comprehensive Loss.

Certain awards deemed to be granted outside of the Company's equity incentive plans require the Company to use liability accounting. These awards are classified as a liability and are remeasured at fair value at the end of each reporting period until such time they are deemed to be granted under the Company's equity incentive plans. Changes in fair value are included in compensation expense in the Consolidated Statements of Comprehensive Loss (see additional disclosures related to awards granted outside of the 2000 Stock Incentive Plan in Note 8, Stock-Based Compensation).

Income Taxes The Company accounts for income taxes under the asset and liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and operating loss carry forwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period that includes the enactment date.

A valuation allowance is recorded to reduce the deferred tax assets to the amount that is expected to be realized. In evaluating the need for a valuation allowance, the Company takes into account various factors, including the expected level of future taxable income and available tax planning strategies. If actual results differ from the assumptions made in the evaluation of a valuation allowance, the Company records a change in valuation allowance through income tax expense in the period such determination is made.

The Company uses a comprehensive model for how it measures, presents and discloses an uncertain tax position taken or expected to be taken in a tax return. The Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained on examination by taxing authorities, based solely on the technical merits of the position. The tax benefits recognized in the financial statements from such a position should be measured based on the largest benefit that has a greater than 50% likelihood to be sustained upon ultimate settlement. The Company has no uncertain tax positions as of December 31, 2014 that qualify for either recognition or disclosure in the consolidated financial statements.

The Company's policy for interest and penalties related to income tax exposures is to recognize interest and penalties as a component of the income taxes on continuing operations in the Consolidated Statements of Comprehensive Loss.

Net Loss Per Common Share Basic net loss per common share is computed by dividing net loss attributable to common stockholders by the weighted average number of common shares outstanding during the period. Diluted net loss per common share is computed by dividing net loss by the weighted average number of common shares and other dilutive securities outstanding during the period.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

Potentially dilutive securities from stock options, restricted stock units and warrants to purchase common stock would be antidilutive as the Company incurred a net loss in all periods presented. Potentially dilutive common shares resulting from the assumed exercise of outstanding stock options and warrants are determined based on the treasury stock method.

The following table sets forth the reconciliation of the weighted average number of shares used to compute basic and diluted net loss per share for the years ended December 31, 2014, 2013 and 2012.

	Years Ended December 31,		
	2014	2013	2012
	(In thousands, except per share amounts)		
Numerator:			
Net loss:	$ (79,159)	$ (56,073)	$ (41,374)
Denominator:			
Weighted average common shares used in calculation of basic net loss per share:	43,095	34,980	26,545
Effect of dilutive securities:			
Common stock options	-	-	-
Restricted stock and restricted stock units	-	-	-
Common stock warrant	-	-	-
Weighted average common shares outstanding used in calculation of diluted net loss per share	43,095	34,980	26,545
Net loss per share:			
Basic and Diluted	$ (1.84)	$ (1.60)	$ (1.56)

The following potentially dilutive securities have been excluded from the computations of diluted weighted-average common shares outstanding as of December 31, 2014, 2013 and 2012 as their effect would have been anti-dilutive (in thousands).

	2014	2013	2012
Warrants to purchase common stock	-	-	330
Stock options to purchase common stock	4,400	3,633	1,818
Restricted stock and restricted stock units	21	93	216

Segment Information The Company currently operates in one business segment, which is the development and commercialization of inhaled therapies for patients with serious lung diseases. A single management team that reports to the Chief Executive Officer comprehensively manages the entire business. The Company does not operate separate lines of business with respect to its products or product candidates. Accordingly, the Company does not have separate reportable segments.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

New Accounting Pronouncements In May 2014, the FASB issued Accounting Standards Update No. 2014-09, *Revenue from Contracts with Customers (Topic 606)*, ("ASU 2014-09"). ASU 2014-09 outlines a new, single comprehensive model for entities to use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance, including industry-specific guidance. This new revenue recognition model provides a five-step analysis in determining when and how revenue is recognized. The new model will require revenue recognition to depict the transfer of promised goods or services to customers in an amount that reflects the consideration a company expects to receive in exchange for those goods or services. ASU 2014-09 is effective for public entities for annual reporting periods beginning after December 15, 2016 and interim periods within those periods. Early adoption is not permitted. Companies may use either a full retrospective or a modified retrospective approach to adopt ASU 2014-09. The Company is currently evaluating the impact this standard will have on its operating results in future periods when revenue is recorded.

3. Accrued Expenses

Accrued expenses consist of the following:

	As of December 31,	
	2014	2013
	(in thousands)	
Accrued clinical trial expenses	$ 2,113	$ 2,484
Accrued technical operation expenses	762	1,220
Accrued construction costs	1,500	-
Accrued professional fees	542	24
Accrued interest payable	258	159
Other accrued expenses	146	18
	$ 5,321	$ 3,905

4. Identifiable Intangible Assets

The Company's only identifiable intangible asset was in-process research and development ("IPRD") related to ARIKAYCE for the NTM and CF indications as of December 31, 2014 and 2013. The total intangible IPRD asset was $58.2 million as of December 31, 2014 and 2013, which resulted from the initial amount recorded at the time of the Company's merger with Transave and subsequent adjustments in the value. Historically, the Company uses the income approach to derive the fair value of in-process research and development assets. This approach calculates fair value by estimating future cash flows attributable to the assets and then discounting these cash flows to a present value using a risk-adjusted discount rate. Identifiable intangible assets are measured at their respective fair values and are not amortized until commercialization. Once commercialization occurs, intangible assets will be amortized over their estimated useful lives. The Company did not identify any indicators of impairment of its in-process research and development intangible assets as of December 31, 2014.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

5. Fixed Assets, net

Fixed assets are stated at cost and depreciated or amortized using the straight-line method, based on useful lives as follows:

Asset Description	Estimated Useful Life (years)	As of December 31, 2014	2013
		(in thousands)	
Lab equipment	7	$ 3,449	$ 3,371
Furniture and fixtures	7	1,127	65
Computer hardware and software	3 - 5	921	718
Office equipment	7	65	117
Manufacturing Equipment	7	669	375
Leasehold improvements	lease term	4,627	612
Construction in Progress (CIP)		-	116
		10,858	5,374
Less accumulated depreciation		(3,324)	(3,562)
Fixed assets, net		$ 7,534	$ 1,812

Depreciation expense was $1.1 million, $0.7 million and $0.6 million for the years ended December 31, 2014, 2013 and 2012, respectively. Depreciation expense includes depreciation for equipment under capital lease obligations.

6. Debt

On June 29, 2012, the Company and its domestic subsidiaries, as co-borrowers, entered into a Loan and Security Agreement with Hercules Technology Growth Capital, Inc. ("Hercules") that allowed the Company to borrow up $20.0 million in $10.0 million increments ("Loan Agreement"). The Company borrowed the first and second $10.0 million increments by signing two Secured Promissory Notes ("Note A" and "Note B" and collectively, the "Notes") on June 29, 2012 and December 27, 2012, respectively. Notes A and B bear interest at 9.25%. Note A was originally scheduled to be repaid over a 42-month period with the first twelve monthly payments representing interest only followed by thirty monthly equal payments of principal and interest. Note B was originally scheduled to be repaid over a 36-month period with the first six monthly payments representing interest only followed by thirty monthly equal payments of principal and interest. The Loan Agreement provided that in certain circumstances the Company could delay the first principal payment by five months. In July 2013, subsequent to the completion of certain ARIKAYCE-related development milestones, the Company elected to extend the interest only period under the Notes from July 31, 2013 to December 31, 2013 and delay the first monthly principal repayments for Notes A and B from August 1, 2013 to January 1, 2014.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

6. Debt (Continued)

On November 25, 2013, the Company and Hercules entered into an amendment (the "First Amendment") of the Loan Agreement. The First Amendment initially extended the interest-only period through June 30, 2014 and called for the first monthly principal payment on July 1, 2014. The First Amendment also allowed the Company to further extend the interest-only period through December 31, 2014 and delay the first payment of principal until January 1, 2015, so long as the Company paid a $100,000 fee and obtained positive data from its phase 2 clinical trial of ARIKAYCE in patients who have lung infections caused by nontuberculous mycobacteria (NTM). In June 2014, the Company paid the $100,000 fee and exercised its option to extend the interest-only period and delay the first payment of principal to January 1, 2015. The election and second amendment did not change the maturity date for Notes A and B, which is January 1, 2016.

On December 15, 2014, Company and Hercules entered into a third amendment (the "Third Amendment") to the Loan Agreement. In connection with the Third Amendment, the Company paid a commitment fee of $25,000, and at the closing, paid a facility fee of $125,000. Under the Third Amendment, the amount of borrowings was increased by $5.0 million to a total of $25.0 million and the interest-only period was extended through December 31, 2015. In addition, in the event the Company receives $90.0 million in cash proceeds from the completion of certain types of equity financings, subordinated debt financings, and/or up-front cash payments from corporate transactions prior to December 31, 2015, the Company will have the option to extend the maturity date of the loan to January 1, 2018. If the Company elects to exercise such option, it must pay Hercules a $250,000 fee.

In connection with the Third Amendment, on December 15, 2014, the Company entered into a stock purchase agreement with Hercules pursuant to which the Company issued 70,771 unregistered shares of its common stock, at a price of $14.13 per share (the closing price of the Company's Common Stock as reported by the NASDAQ Stock Market on December 12, 2014), for an aggregate purchase price of approximately $1.0 million. See Note 7 for more information related to the shares purchased under the stock purchase agreement with Hercules.

In connection with the Loan Agreement, the Company granted the lender a first position lien on all of the Company's assets, excluding intellectual property. Prepayment of the loans made pursuant to the Loan Agreement is subject to penalty and the Company is required to pay an "end of term" charge of $390,000, which is being charged to interest expense (and accreted to the debt) using the effective interest method over the life of the Loan Agreement. If the Company exercises its option to extend the maturity of the debt to January 1, 2018, the end of term charge will be due on January 1, 2016. Debt issuance fees paid to the lender were recorded as a discount on the debt and are being amortized to interest expense using the effective interest method over the life of the Loan Agreement. Debt issuance fees paid to third parties were capitalized and are being amortized to interest expense using the effective interest method over the life of the Loan Agreement.

The Loan Agreement also contains representations and warranties by us and the lender and indemnification provisions in favor of the lender and customary covenants (including limitations on other indebtedness, liens, acquisitions, investments and dividends, but no financial covenants), and events of default (including payment defaults, breaches of covenants following any applicable cure period, a material impairment in the perfection or priority of the lender's security interest or in the collateral, and events relating to bankruptcy or insolvency). Upon the occurrence of an event of default,

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

6. Debt (Continued)

a default interest rate of an additional 5% may be applied to the outstanding loan balances, and the lender may terminate its lending commitment, declare all outstanding obligations immediately due and payable, and take such other actions as set forth in the Loan Agreement. In addition, pursuant to the Loan Agreement, the lender has the right to participate, in an amount of up to $1.0 million, in certain future private equity financing(s) by the Company.

In conjunction with entering into the original Loan Agreement in 2012, the Company granted a warrant to the lender to purchase shares of the Company's common stock. Since the warrant was granted in conjunction with entering into the Loan Agreement, the relative fair value of the warrant was recorded as equity and debt discount. On April 30, 2013, the lender exercised the warrant in full. The debt discount is being amortized to interest expense over the term of the related debt using the effective interest method.

The following table presents the components of the Company's debt balance as of December 31, 2014:

	December 31, 2014 (in thousands)
Debt:	
Notes payable	$ 25,000
Accretion of end of term charge	314
Issuance fees paid to lender	(308)
Discount from warrant	(150)
Current portion of long-term debt	-
Long-term debt	$ 24,856

Future principal repayments of the Company's long-term debt are as follows (in thousands):

Year Ending in December 31:	
2015	$ -
2016	25,000
	$ 25,000

The estimated fair value of the debt (categorized as a Level 2 liability for fair value measurement purposes) is determined using current market factors and the ability of the Company to obtain debt at comparable terms to those that are currently in place. As of December 31, 2014, the fair value of the Company's debt approximates the carrying amount.

7. Stockholders' Equity

Common Stock As of December 31, 2014, the Company had 500,000,000 shares of common stock authorized with a par value of $0.01 and 49,806,131 shares of common stock issued and

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

7. Stockholders' Equity (Continued)

outstanding. In addition, as of December 31, 2014, the Company had reserved 4,400,106 shares of common stock for issuance upon the exercise of outstanding common stock options and 20,502 for issuance upon the vesting of restricted stock units.

On December 15, 2014, in connection with the Third Amendment to the Loan Agreement, the Company entered into a stock purchase agreement with Hercules pursuant to which the Company issued 70,771 shares of its common stock, at a price of $14.13 per share (the closing price of the Company's Common Stock as reported by the NASDAQ Stock Market on December 12, 2014), for an aggregate purchase price of approximately $1.0 million. The securities sold in this private placement have not been registered under the Securities Act of 1933, as amended (the "Act") and may not be offered or sold in the United States in the absence of an effective registration statement or exemption from the registration requirements under the Act. The issuance of the securities in this transaction were exempt from registration under Section 4(2) of the Securities Act of 1933.

On August 18, 2014, the Company completed an underwritten public offering of 10,235,000 shares of the Company's common stock, which included the underwriter's exercise in full of its over-allotment option of 1,335,000 shares, at a price to the public of $11.25 per share. The Company's net proceeds from the sale of the shares, after deducting the underwriter's discount and offering expenses of $7.1 million, were $108.0 million.

On July 22, 2013, the Company completed an underwritten public offering of 6,900,000 shares of the Company's common stock, which included the underwriter's exercise in full of its over-allotment option of 900,000 shares, at a price to the public of $10.40 per share. The Company's net proceeds from the sale of the shares, after deducting the underwriter's discount and offering expenses of $4.7 million, were $67.0 million.

On September 28, 2012, the Company completed a registered direct public offering of 6,304,102 shares of the Company's common stock to certain investors at a price of $4.07 per share, resulting in proceeds of $25.7 million.

Preferred Stock As of December 31, 2014 and 2013, the Company had 200,000,000 shares of preferred stock authorized with a par value of $0.01 and no shares of preferred stock were issued and outstanding.

Warrant In conjunction with entering into the Loan Agreement in 2012 (See Note 6 Debt), the Company granted a warrant to the lender to purchase 329,932 shares of the Company's common stock at an exercise price of $2.94 per share. The fair value of the warrant of $0.8 million was calculated using the Black-Scholes warrant-pricing methodology at the date of issuance and was recorded as equity and as a discount to the debt and was amortized to interest expense over the term of the related debt using the effective interest method. On April 30, 2013, the lender exercised the warrant in full via the "net issuance" method specified in the warrant agreement. In accordance with such provisions, the Company issued and delivered 223,431 shares of common shares to the lender on May 1, 2013. As a result of the exercise, the warrant is no longer outstanding and there are no additional shares issuable under this instrument.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation

The Company currently has one equity compensation plan, the 2013 Incentive Plan, which was approved by shareholders at the Company's Annual Meeting of Shareholders on May 23, 2013 (the "2013 Incentive Plan"). The 2013 Incentive Plan is administered by the Compensation Committee and the Board of Directors of the Company. Under the terms of the 2013 Incentive Plan, the Company is authorized to grant a variety of incentive awards based on its common stock, including stock options (both incentive stock options and non-qualified stock options), performance options/shares and other stock awards, as well as the payment of incentive bonuses to all employees and non-employee directors. The 2013 Incentive Plan provides for the issuance of a maximum of 3,053,833 shares of common stock. Shares subject to outstanding awards under the 2000 Stock Incentive Plan that are cancelled, expired, forfeited or otherwise not issued will also be added to the number of shares available under the 2013 Incentive Plan. As of December 31, 2014, 508,062 shares of the Company's common stock were reserved for future grants (or issuances) of restricted stock, restricted stock units, stock options, and stock warrants under the 2013 Incentive Plan. The 2013 Incentive Plan will terminate on April 16, 2023 unless it is extended or terminated earlier pursuant to its terms.

During 2013, the Company had three equity compensation plans: the 2013 Incentive Plan, the Amended and Restated 2000 Stock Incentive Plan, as amended (the "2000 Stock Incentive Plan") and the Amended and Restated 2000 Employee Stock Purchase Plan (the "Stock Purchase Plan"). Both the 2000 Stock Incentive Plan and the Stock Purchase Plan were adopted by the Company's Board of Directors in 2000. Upon the approval of the 2013 Incentive Plan, no additional awards were issued under the 2000 Stock Incentive Plan and the shares remaining for future grant under the 2000 Stock Incentive Plan were transferred to the 2013 Incentive Plan.

During the first quarter of 2013, the Company completed a review of equity compensation awards granted under its 2000 Stock Incentive Plan and determined that it had inadvertently exceeded the annual per-person sub-limits involving certain awards previously made to certain of its current and past officers and directors (the "excess awards"). The aggregate amount of common stock represented by these excess awards, which consisted of RSUs and stock options, was approximately 1.4 million shares. These awards were deemed to be granted outside of the 2000 Stock Incentive Plan and as such the Company applied liability accounting to these awards. On May 23, 2013 (the date of the Company's 2013 Annual Meeting of Stockholders), shareholders approved the grants associated with the excess awards, which as of this date, allowed the excess awards to be deemed granted under the 2000 Stock Incentive Plan. As a result, the excess awards were re-measured at fair value on May 23, 2013 and the liability was reclassified to additional paid-in capital. The unrecognized fair value calculated for the excess awards as of May 23, 2013 will be recognized as compensation expense ratably over the remaining requisite service period for each award.

Stock Options The Company calculates the fair value of stock options granted using the Black-Scholes valuation model. The Company calculated the fair value of stock options granted outside of the 2000 Stock Incentive Plan using liability accounting. These awards were classified as a liability and were re-measured at fair value at the end of each reporting period using the Black-Scholes valuation model and changes in fair value were included in compensation expense in the Consolidated Statements of Comprehensive Loss (see additional disclosures related to stock options granted outside the 2000 Stock Incentive Plan at the end of this footnote).

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

The following table summarizes the grant date fair value and assumptions used in determining the fair value of stock options granted under and outside the 2013 Incentive Plan and the 2000 Stock Incentive Plan, as well as grants of inducement shares, during the years ended December 31, 2014, 2013 and 2012.

	2014	2013	2012
Volatility	83% - 86%	86% - 96%	99% - 107%
Risk-free interest rate	1.46% - 1.83%	0.65% - 1.65%	0.57% - 0.99%
Dividend yield	0.0%	0.0%	0.0%
Expected option term (in years)	6.25	6.25	6.25
Weighted-average fair value of stock options granted	$11.74	$8.16	$3.21

For the years ended December 31, 2014, 2013 and 2012, the volatility factor was based on the Company's historical volatility since the closing of the Merger on December 1, 2010. The expected life was determined using the simplified method as described in ASC Topic 718, "Accounting for Stock Compensation", which is the midpoint between the vesting date and the end of the contractual term. The risk-free interest rate was based on the US Treasury yield in effect at the date of grant. Forfeitures are based on actual percentage of option forfeitures since the closing of the Merger on December 1, 2010, and this is the basis for future forfeiture expectations.

From time to time, the Company grants performance-condition options to certain employees. Vesting of these options is subject to the Company achieving certain performance criteria established at the date of grant and the individuals fulfilling a service condition (continued employment). As of December 31, 2014, the Company had performance options totaling 396,667 shares outstanding. As a result of the Marketing Authorization Application ("MAA") acceptance for ARIKAYCE, which was received from the European Medicines Agency ("EMA") in February 2015, performance options totaling $1.5 million will be recorded as non-cash compensation expense in the first quarter of 2015.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

The following table summarizes stock option activity for stock options granted under the 2013 Incentive Plan and the 2000 Stock Incentive Plan, as well as grants of inducement shares, for the years ended December 31, 2014, 2013 and 2012 as follows:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life in Years	Aggregate Intrinsic Value (in '000)
Options outstanding at December 31, 2011	891,751	$ 5.15		
Granted	1,116,384	4.12		
Exercised	(30,250)	7.08		
Forfeited and expired	(160,046)	9.54		
Options outstanding at December 31, 2012	1,817,839	4.10		
Vested and expected to vest at December 31, 2012	1,692,915	4.11		
Exercisable at December 31, 2012	438,145	4.59		
Options outstanding at December 31, 2012	1,817,839	$ 4.10		
Granted	2,323,500	10.53		
Exercised	(371,743)	4.37		
Forfeited and expired	(136,600)	10.49		
Options outstanding at December 31, 2013	3,632,996	7.94		
Vested and expected to vest at December 31, 2013	3,402,306	7.88		
Exercisable at December 31, 2013	484,213	4.25		
Options outstanding at December 31, 2013	3,632,996	$ 7.94		
Granted	1,600,452	16.10		
Exercised	(283,057)	6.11		

Forfeited and expired	(550,285)	11.42			
Options outstanding at December 31, 2014	4,400,106	10.59	8.47	$	24,172
Vested and expected to vest at December 31, 2014	3,891,511	10.32	8.43	$	22,304
Exercisable at December 31, 2014	1,235,710	6.90	7.94	$	10,597

The total intrinsic value of stock options exercised during the years ended December 31, 2014, 2013 and 2012 was $2.5 million, $2.7 million and $0, respectively.

As of December 31, 2014, there was $24.0 million of unrecognized compensation expense related to unvested stock options, which is expected to be recognized over a weighted average period of 2.4 years. Included above in unrecognized compensation expense was $3.2 million related to

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

outstanding performance-based options. The following table summarizes the range of exercise prices and the number of stock options outstanding and exercisable as of December 31, 2014:

Outstanding as of December 31, 2014					Exercisable as of December 31, 2014	
Range of Exercise Prices		Number of Options	Weighted Average Remaining Contractual Term (in years)	Weighted Average Exercise Price	Number of Options	Weighted Average Exercise Price
$ 3.03	$ 3.29	180,804	6.97	$ 3.05	132,114	$ 3.04
$ 3.40	$ 3.40	708,314	7.69	$ 3.40	354,158	$ 3.40
$ 3.60	$ 6.90	737,098	7.93	$ 6.17	358,968	$ 6.15
$ 6.96	$ 11.81	426,325	8.41	$ 9.54	116,738	$ 9.22
$ 12.44	$ 12.44	506,915	8.39	$ 12.44	138,557	$ 12.44
$ 12.58	$ 12.58	581,300	9.42	$ 12.58	25,000	$ 12.58
$ 12.66	$ 14.24	443,300	9.03	$ 13.83	73,750	$ 14.06
$ 14.32	$ 19.40	444,750	9.10	$ 17.25	36,425	$ 15.48
$ 19.88	$ 20.49	356,300	9.03	$ 20.46	-	-
$ 21.54	$ 21.54	15,000	9.05	$ 21.54	-	-

Restricted Stock and Restricted Stock Units The Company may grant Restricted Stock ("RS") and Restricted Stock Units ("RSUs") to employees and non-employee directors. Each RS and RSU represents a right to receive one share of the Company's common stock upon the completion of a specific period of continued service or achievement of a certain milestone. RS and RSU awards granted under the Company's 2013 Incentive Plan and 2000 Stock Incentive Plan are valued at the market price of the Company's common stock on the date of grant. The Company recognizes noncash compensation expense for the fair values of these RS and RSUs on a straight-line basis over the requisite service period of these awards.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

The following table summarizes RSU awards granted under the 2013 Incentive Plan and the 2000 Stock Incentive Plan during the years ended December 31, 2014, 2013 and 2012:

	Number of RSU's	Weighted Average Grant Price
Outstanding at December 31, 2011	487,025	$ 6.37
Granted	61,011	3.44
Released	(322,819)	4.59
Forfeited	(9,692)	5.69
Outstanding at December 31, 2012	215,525	$ 6.26
Granted	55,317	6.77
Released	(177,316)	6.42
Forfeited	(885)	5.00
Outstanding at December 31, 2013	92,641	$ 6.27
Granted	20,502	19.47
Released	(92,641)	6.27
Forfeited	-	-
Outstanding at December 31, 2014	20,502	$ 19.47
Expected to Vest	20,502	$ 19.47

Awards Granted Outside of the 2000 Stock Incentive Plan As described above, during the first quarter of 2013, the Company completed a review of equity compensation awards granted under its 2000 Stock Incentive Plan and determined that it had inadvertently exceeded the annual per-person sub-limits involving certain awards previously made to certain of its current and past officers and directors (the "excess awards"). The aggregate amount of common stock represented by these excess awards, which consisted of RSUs and stock options, was approximately 1.4 million shares. These awards were deemed to be granted outside of the 2000 Stock Incentive Plan and as such the Company applied liability accounting to these awards. On May 23, 2013 (the date of the Company's 2013 Annual Meeting of Stockholders), shareholders approved the grants associated with the excess awards, which as of this date, allowed the excess awards to be deemed granted under the 2000 Stock Incentive Plan. As a result, the excess awards were re-measured at fair value on May 23, 2013 and the liability was reclassified to additional paid-in capital. The unrecognized fair value calculated for the excess awards as of May 23, 2013 will be recognized as compensation expense ratably over the remaining requisite service period for each award.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

The following table summarizes the stock-based compensation recorded in the Consolidated Statements of Comprehensive Loss related to stock options and RSUs during the years ended December 31, 2014, 2013 and 2012:

	2014	2013	2012
		(in millions)	
Research and development expenses	$ 4.5	$ 2.4	$ 0.7
General and administrative expenses	6.8	6.3	2.3
Total	$ 11.3(1)	$ 8.7(1)	$ 3.0

(1) Includes $2.4 and $4.1 million for the years ended December 31, 2014 and 2013, respectively, for the remeasurement of certain stock options and RSUs that occurred during May 2013.

9. Income Taxes

The benefit for income taxes was $10.4 million and $1.2 million and the effective rates were approximately 12% and 2% for the years ended December 31, 2014 and 2013, respectively. The provision for income taxes was $0 and the effective rate was 0.0% during the year ended December 31, 2012. The benefit for income taxes recorded and the effective tax rates for the year ended December 31, 2014 and 2013 solely reflect the reversal of valuation allowances previously recorded against the Company's New Jersey State net operating losses ("NOL") that resulted from the Company's sale of $110.5 million and $27.0 million of its New Jersey State NOLs under the State of New Jersey's Technology Business Tax Certificate Transfer Program (the "Program") for cash of $10.4 million and $1.2 million, respectively, net of commissions. The Program allows qualified technology and biotechnology businesses in New Jersey to sell unused amounts of NOLs and defined research and development tax credits for cash.

The Company is subject to US federal and state income taxes. The Company has never been audited and the statute of limitations for tax audit is open for the federal tax returns for the years ended 2011 and later and is generally open for certain states for the years 2010 and later. However, except in 2009, the Company has incurred net operating losses since inception. Such loss carryforwards would be subject to audit in any tax year in which those losses are utilized, notwithstanding the year of origin. The Company's policy is to recognize interest accrued related to unrecognized tax benefits and penalties in income tax expense. The Company has recorded no such expense. As of December 31, 2014 and 2013, the Company has recorded no reserves for unrecognized income tax benefits, nor has it recorded any accrued interest or penalties related to uncertain tax positions. The Company does not anticipate any material changes in the amount of unrecognized tax positions over the next twelve months.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

9. Income Taxes (Continued)

The reconciliation between the federal statutory tax rate of 34% and the Company's effective tax rate is as follows:

	Years Ended December 31,		
	2014	**2013**	**2012**
Statutory federal tax rate	34%	34%	34%
Permanent items	(3)%	0%	0%
State income taxes, net of federal benefit	(7)%	7%	4%
R&D and other tax credits	5%	7%	1%
Expired net operating loss carryforwards	0%	0%	(15)%
Change in state tax rate	0%	2%	0%
Change in valuation allowance	(17)%	(49)%	(22)%
Other	0%	1%	(2)%
Effective tax rate	12%	2%	0%

Deferred tax assets and liabilities are determined based on the difference between financial statement and tax bases using enacted tax rates in effect for the year in which the differences are expected to reverse. The components of the deferred tax assets and liabilities consist of the following:

	As of December 31,	
	2014	**2013**
	(in thousands)	
Deferred tax assets:		
Net operating loss carryforwards	$ 160,758	$ 149,753
General business credits	18,150	15,209
Alternative minimum tax (AMT) credit	418	418
Other	7,863	5,951
Gross deferred tax assets	$ 187,189	$ 171,331
Deferred tax liabilities:		
In-process research and development	$ (23,245)	$ (23,245)
Deferred tax liabilities	$ (23,245)	$ (23,245)
Net deferred tax assets	$ 163,944	$ 148,086
Valuation allowance	(163,944)	(148,086)
Net deferred tax assets	$ -	$ -

The net deferred tax assets (prior to applying the valuation allowance) of $163.9 million and $148.1 million at December 31, 2014 and 2013, respectively, primarily consist of net operating loss carryforwards for income tax purposes. Due to the Company's history of operating

losses, the Company recorded a full valuation allowance on its net deferred tax assets by increasing the valuation allowance by $15.8 million in 2014 as it is more likely than not that such tax benefits will not be realized.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

9. Income Taxes (Continued)

At December 31, 2014, the Company had federal net operating loss carryforwards for income tax purposes of approximately $461.8 million. Due to the limitation on NOLs as more fully discussed below, $283.5 million of the NOLs are available to offset future taxable income, if any. The NOL carryovers and general business tax credits expire in various years beginning in 2018. For state tax purposes, the Company has approximately $63 million of New Jersey NOLs available to offset against future taxable income or to be sold as part of the New Jersey Transfer Program. The Company also has California and Virginia NOLs that are entirely limited due to Section 382 (as discussed below), in addition to changing state apportionment allocations, as the Company is now 100% resident in New Jersey.

During 2014, the Company completed an Internal Revenue Code Section 382 ("Section 382") analysis in order to determine the amount of losses that are currently available to offset against future taxable income, if any. It was determined that the utilization of the Company's NOL and general business tax credit carryforwards generated in tax periods up to and including December 2010 (the "December 2010 and prior NOLs") were subject to substantial limitations under Section 382 due to ownership changes that occurred at various points from its original organization through December 2010. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain shareholders or public groups in the stock of a corporation by more than 50 percentage points over a three-year period. Since the Company's formation, it has raised capital through the issuance of common stock on several occasions which, combined with the purchasing shareholders' subsequent disposition of those shares, resulted in multiple changes in ownership, as defined by Section 382 since the Company's formation in 1999. These ownership changes resulted in substantial limitations on the use of the Company's NOLs and general business tax credit carryforwards up to and including December 2010. The Company continues to track all of its NOLs and tax credit carryforwards but has provided a full valuation allowance to offset those amounts.

10. License and Collaboration Agreements

In-License Agreements

PARI Pharma GmbH In April 2008, the Company entered into a licensing agreement with PARI Pharma GmbH ("PARI") for use of the optimized eFlow Nebulizer System for delivery of ARIKAYCE in treating patients with NTM infections, CF and bronchiectasis. The Company has rights to several US and foreign issued patents and patent applications involving improvements to the optimized eFlow Nebulizer System. Under the licensing agreement, PARI is entitled to receive payments either in cash, qualified stock or a combination of both, at PARI's discretion, based on achievement of certain future milestone events including first acceptance of MAA submission (or equivalent) in the US of ARIKAYCE and the device, first receipt of marketing approval in the US for ARIKAYCE and the device, and first receipt of marketing approval in a major EU country for ARIKAYCE and the device. In addition, PARI is entitled to receive royalty payments on commercial sales of ARIKAYCE. See below for information related to the commercialization agreement with PARI.

Out-License Agreements

NAPO Pharmaceuticals In January 2007, the Company entered into an agreement with NAPO Pharmaceuticals, whereby it granted NAPO a license for INSM-18 also known as Masoprocal. The

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

10. License and Collaboration Agreements (Continued)

license gives NAPO the right to develop, manufacture and commercialize Masoprocal products for any indications relating specifically to diabetes, cardiac disease, vascular disease, metabolic disease and Syndrome X. The agreement calls for payments from NAPO to the Company upon the achievement of certain milestones which have not yet been met.

TriAct In December 2010, the Company entered into an agreement with TriAct Therapeutics Inc. ("TriAct") whereby it granted TriAct an exclusive license for INS-18 also known as Masoprocal. The license gives TriAct the right to develop, manufacture and commercialize Masoprocal products for any indications relating specifically to oncology. The agreement calls for the issue of TriAct common stock to Insmed upon the achievement of certain milestones. To date, no milestones have been achieved and no common stock has been received.

Eleison In February 2011, the Company entered into an agreement with Eleison Pharmaceuticals whereby it granted Eleison an exclusive license for CISPLATIN Lipid Complex. The license gives Eleison the right to develop, manufacture and commercialize CISPLATIN Lipid Complex. Payments totaling $1.0 million were received in 2011 and were recorded as license fee revenue.

Premacure (now Shire plc) In May 2012, the Company entered into an agreement with Premacure (now Shire plc) pursuant to which the Company granted to Premacure an exclusive, worldwide license to develop, manufacture and commercialize IGF-1, with its natural binding protein, IGFBP-3, for the prevention and treatment of complications of preterm birth in exchange for royalty payments on commercial sales of IGF-1 (the "Premacure License Agreement"). In March 2013, the Company amended the Premacure License Agreement to provide Premacure with the option, exercisable by Premacure any time prior to April 30, 2013, to pay the Company $11.5 million (the "Buyout Amount") and assume any of the Company's royalty obligations to other parties in exchange for a fully paid license. On April 29, 2013, Premacure exercised this option and paid the Company $11.5 million in exchange for a fully paid license. The Company recorded this payment as other revenue in the three months ended June 30, 2013. The Company is not entitled to any additional future royalties from Premacure, and Premacure has assumed the Company's royalty obligations to other parties under the Premacure License Agreement.

Collaboration Agreements

Cystic Fibrosis Foundation Therapeutics, Inc. In 2004 and 2009, the Company entered into research funding agreements with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) whereby it received $1.7 million and $2.2 million for each respective agreement in research funding for the development of its ARIKAYCE product. If ARIKAYCE becomes an approved product for CF in the US, the Company will owe payments totaling up to $13.4 million to CFFT that would be payable over a three-year period after approval as a commercialized drug in the US. Furthermore, if certain global sales milestones are met within 5 years of the drug commercialization, the Company would owe an additional payment of $3.9 million. Since there is significant development risk associated with ARIKAYCE, the Company has not accrued these obligations.

National Institutes of Allergy and Infectious Diseases In 2009 and 2012, the Company entered into a cooperative research and development agreement (CRADA) with National Institute of Allergy

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

10. License and Collaboration Agreements (Continued)

and Infectious Diseases (NIAID) to design and conduct the Company's phase 2 study of ARIKAYCE in patients with NTM. NIAID has also agreed to provide biostatistical advisory input in connection with the phase 2 NTM study. If the Company decides not to continue with the commercialization of ARIKAYCE in NTM, NIAID will have the right to complete the clinical trial. Further, NIAID may elect to pursue its rights to obtain license rights to certain inventions made under the CRADA.

Therapure Biopharma Inc. In February 2014, the Company entered into a Contract Manufacturing Agreement with Therapure Biopharma Inc. ("Therapure") for the manufacture of the Company's product ARIKAYCE. Pursuant to the agreement, the Company and Therapure are collaborating to construct a production area for the manufacture of ARIKAYCE in Therapure's existing manufacturing facility in Mississauga, Ontario, Canada. Therapure will manufacture ARIKAYCE for the Company on a non-exclusive basis. The agreement has an initial term of five years from the first date on which Therapure delivers ARIKAYCE to Insmed after Insmed obtains permits related to the manufacture of ARIKAYCE, and will renew automatically for successive periods of two years each, unless terminated by either party by providing the required two years' prior written notice to the other party. Notwithstanding the foregoing, the parties have rights and obligations under the agreement prior to the commencement of the initial term. The agreement allows for termination by either party upon the occurrence of certain events, including (i) the material breach by the other party of any provision of the agreement or the quality agreement expected to be entered into between the parties, or (ii) the default or bankruptcy of the other party. In addition, the Company may terminate the agreement for any reason upon no fewer than one hundred eighty days' advance notice. Costs incurred under this agreement will be recorded as a component of research and development expense until such time as the Company receives regulatory approvals for ARIKAYCE.

PARI Pharma GmbH In July 2014, the Company entered into a Commercialization Agreement with PARI for the manufacture and supply of eFlow nebulizer device as optimized for use with the Company's proprietary liposomal amikacin for inhalation. The agreement has an initial term of fifteen years from the first commercial sale of the device (the "Initial Term"). The term of the agreement may be extended by the Company for an additional five years by providing written notice to PARI at the least one year prior to the expiration of the Initial Term. Notwithstanding the foregoing, the parties have certain rights and obligations under the agreement prior to the commencement of the Initial Term. The agreement allows for termination by either party upon the occurrence of certain events, including (i) the material breach by the other party of any provision of the agreement, (ii) the default or bankruptcy of the other party, or (iii) upon termination by the Company of the License Agreement between the parties.

SynteractHCR, Inc. In December 2014, the Company, entered into Work Order 1, pursuant to a Master Agreement for services with SynteractHCR, Inc., ("Synteract"), dated as of August 27, 2014, as amended on December 23, 2014, pursuant to which the Company retained Synteract to perform implementation and management services in connection with certain clinical trials pursuant to a specific protocol of pharmaceutical products under development by or under the control of the Company. Synteract is providing comprehensive services for the 212 study. Prior to the execution of the Work Order, Synteract was providing such services pursuant to a Letter of Intent, dated August 25, 2014. The Work Order covers services related to the 212 study only and any additional Study will be subject to the negotiation and execution of an additional work order.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

11. Commitments and Contingencies

Commitments

The Company has an operating lease for office and laboratory space located in Bridgewater, NJ that terminates in November 2019. Future minimum rental payments under this lease are $3.5 million. The Company also leases office space in Richmond, VA, where the Company's corporate headquarters were previously located, through October 2016. Future minimum rental payments under this lease total approximately $0.9 million. During 2011, the Company recorded a net present value charge of $1.2 million in general and administrative expenses associated with vacating the Richmond facility. The remaining accrual for this charge was $0.4 million as of December 31, 2014. In December 2014, the Company entered into an agreement to sublet this space for the remainder of the lease term.

Rent expense charged to operations, net of rental income recorded, was $1.3 million, $1.0 million, and $1.0 million for the years ended December 31, 2014, 2013 and 2012, respectively. Future minimum rental payments required under the Company's operating leases are as follows (in thousands):

Year Ending in December 31:	
2015	$ 1,106
2016	1,144
2017	741
2018	762
2019	718
	$ 4,471

Legal Proceedings

From time to time, the Company is a party to various other lawsuits, claims and other legal proceedings that arise in the ordinary course of business. While the outcomes of these matters are uncertain, management does not expect that the ultimate costs to resolve these matters will have a material adverse effect on the Company's consolidated financial position, results of operations or cash flows.

12. Quarterly Financial Data (Unaudited)

The following table summarizes unaudited quarterly financial data for the years ended December 31, 2014 and 2013 (in thousands, except per share data).

	2014				
	First Quarter	**Second Quarter**	**Third Quarter**	**Fourth Quarter**	**Total**
Revenues	$ -	$ -	$ -	$ -	$ -
Operating loss	$ (18,079)	$ (22,816)	$ (23,404)	$ (23,066)	$ (87,365)
Net loss	$ (14,298)	$ (23,224)	$ (23,990)	$ (17,647)	$ (79,159)
Basic and diluted net loss per share	$ (0.36)	$ (0.59)	$ (0.54)	$ (0.36)	$ (1.84)

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

12. Quarterly Financial Data (Unaudited) (Continued)

	2013				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
Revenues	$ -	$ 11,500	$ -	$ -	$ 11,500
Operating loss	$ (14,309)	$ (8,270)	$ (16,842)	$ (15,594)	$ (55,015)
Net loss	$ (13,678)	$ (8,854)	$ (17,327)	$ (16,214)	$ (56,073)
Basic and diluted net loss per share	$ (0.43)	$ (0.28)	$ (0.46)	$ (0.41)	$ (1.60)

Basic and diluted net loss per share amounts included in the above table were computed independently for each of the quarters presented. Accordingly, the sum of the quarterly basic and diluted net loss per share amounts may not agree to the total for the year.

13. Retirement Plan

The Company has a 401(k) defined contribution plan for the benefit for all employees and permits voluntary contributions by employees subject to IRS-imposed limitations. There were no employer contributions in 2014, 2013 and 2012.

14. Subsequent Events

In February 2015, the Company received notification that its MAA was validated after the EMA's pediatric committee approved the pediatric investigation plan for ARIKAYCE. As a result, the Company will record approximately $1.5 million of non-cash compensation expense related to certain performance-based stock options which will vest in the first quarter of 2015. The Company has evaluated all events and transactions since December 31, 2014 through the date of this report.

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EXHIBIT INDEX

2.1	Agreement and Plan of Merger, dated December 1, 2010, among Insmed Incorporated, River Acquisition Co., Transave, LLC Transave, Inc. and TVM V Life Science Ventures GmbH & Co. KG (incorporated by reference from Exhibit 2.1 to Insmed Incorporated's Current Report on Form 8-K filed on December 2, 2010).
3.1	Articles of Incorporation of Insmed Incorporated, as amended through June 14, 2012 (incorporated by reference from Exhibit 3.1 to Insmed Incorporated's Annual Report on Form 10-K for the year ended December 31, 2012).
3.2	Amended and Restated Bylaws of Insmed Incorporated (incorporated by reference from Exhibit 3.1 to Insmed Incorporated's Current Report on Form 8-K filed on March 9, 2012).
4.1	Specimen stock certificate representing common stock, $0.01 par value per share, of the Registrant (previously filed as Exhibit 4.2 to Insmed Incorporated's Registration Statement on Form S-4/A (Registration No. 333-30098)).
10.1**	Insmed Incorporated Amended and Restated 2000 Stock Incentive Plan (incorporated by reference from Exhibit 10.3 to Insmed Incorporated's Form 10-Q filed on May 7, 2013).
10.2**	Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 99.1 to Insmed Incorporated's Registration Statement on Form S-8 filed on May 24, 2013).
10.3**	Form of Award Agreement for Restricted Stock Units issued to employees pursuant to Insmed's 2013 Incentive Plan (incorporated by reference from Exhibit 10.3 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.4**	Form of Award Agreement for Restricted Stock Units issued to directors pursuant to Insmed's 2013 Incentive Plan (incorporated by reference from Exhibit 10.4 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.5**	Form of Award Agreement for an Incentive Stock Option pursuant to Insmed's 2013 Incentive Plan (incorporated by reference from Exhibit 10.5 to Insmed Incorporated's Form 10-K filed on March 6, 2014
10.6**	Form of Award Agreement for a Non-Qualified Stock Option pursuant to Insmed's 2013 Incentive Plan (incorporated by reference from Exhibit 10.6 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.7**	Employment Agreement, dated December 2, 2010, between Insmed Incorporated and Dr. Renu Gupta (incorporated by reference from Exhibit 10.4 to Insmed Incorporated's Current Report on Form 8-K filed on February 1, 2011).
10.8**	Transition and Separation Agreement, dated March 26, 2014 and effective as of April 16, 2014, between Insmed Incorporated and Renu Gupta, M.D. (incorporated by reference from Exhibit 10.3 to Insmed Incorporated's Form 10-Q filed on May 8, 2014).
10.9**	Employment Agreement, effective as of July 18, 2011, between Insmed Incorporated and Andrea Holtzman Drucker (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on July 18, 2011).

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10.10**	Letter Agreement between Insmed Incorporated and Andrea Holtzman Drucker, dated May 28, 2013 (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on May 29, 2013).
10.11**	Employment Agreement, effective as of May 14, 2012, between Insmed Incorporated and Donald Hayden, Jr. (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on May 17, 2012).
10.12**	Letter Agreement, dated September 10, 2012, between Insmed Incorporated and Donald Hayden, Jr. (incorporated by reference from Exhibit 10.3 to Insmed Incorporated's Current Report on Form 8-K filed on September 11, 2012).
10.13**	Employment Agreement, effective as of September 10, 2012, between Insmed Incorporated and William Lewis (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on September 11, 2012).
10.14**	Employment Agreement, effective as of November 7, 2012, between Insmed Incorporated and Andrew Drechsler (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on November 7, 2012).
10.15	Loan and Security Agreement, dated as of June 29, 2012, by and between Insmed Incorporated and its domestic subsidiaries and Hercules Technology Growth Capital, Inc. (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on July 2, 2012).
10.16*	Settlement, license and development agreement, dated March 5, 2007, between Insmed Incorporated, Insmed Therapeutic Proteins, Inc., Celtrix Pharmaceuticals, Tercica Inc., and Genentech, Inc. (previously filed as Exhibit 10.1 to Insmed's Quarterly Report on 10-Q filed on May 10, 2007, and incorporated herein by reference).
10.17*	License agreement dated April 25, 2008, between Transave, Inc. and PARI Pharma GmbH (incorporated by reference from Exhibit 10.22 to Insmed Incorporated's Annual Report on Form 10-K for the year ended December 31, 2012).
10.18**	Employment Agreement, effective as of April 1, 2013, between Insmed Incorporated and Matthew Pauls (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on May 7, 2013).
10.19**	Insmed Incorporated Stock Option Inducement Awards to Matthew Pauls (incorporated by reference from Exhibit 99.2 to Insmed Incorporated's Registration Statement on Form S-8 filed on May 24, 2013).
10.20**	Employment Agreement, effective as of July 29, 2013, between Insmed Incorporated and Christine Pellizzari (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on November 5, 2013).
10.21**	Insmed Incorporated Senior Executive Bonus Plan (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on November 5, 2013).

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10.22	Lease, dated December 31, 2013, between Denver Road, LLC and Insmed Incorporated (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on January 3, 2014).
10.23	Form of Indemnification Agreement entered into with each of the Company's directors and officers (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on January 16, 2014).
10.24+	Contract Manufacturing Agreement, dated February 7, 2014, between Insmed Incorporated and Therapure Biopharma Inc. (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on May 8, 2014).
10.25+	Amending Agreement, dated March 13, 2014, between Insmed Incorporated and Therapure Biopharma Inc. (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on May 8, 2014).
10.26+	Commercialization Agreement dated July 8, 2014 between Insmed Incorporated and PARI Pharma GmbH (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on November 6, 2014).
10.27	Amendment No. 3 to Loan and Security, dated as of December 15, 2014, by and between Insmed Incorporated and its domestic subsidiaries and Hercules Technology Growth Capital, Inc. (filed herewith).
10.28	Stock Purchase Agreement, dated as of December 15, 2014, by and between Insmed Incorporated and Hercules Technology Growth Capital, Inc. (filed herewith).
10.29*	Master Agreement for Services, dated as of August 27, 2014, by and between Insmed Incorporated and SynteractHCR, Inc. (filed herewith).
10.30*	Work Order 1, dated as of December 30, 2014, by and between Insmed Incorporated and SynteractHCR, Inc. (filed herewith).
21.1	Subsidiaries of Insmed Incorporated (filed herewith).
23.1	Consent of Ernst & Young LLP.
31.1	Certification of William H. Lewis, Chief Executive Officer of Insmed Incorporated, pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes Oxley Act of 2003.
31.2	Certification of William H. Lewis, Chief Executive Officer of Insmed Incorporated, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes Oxley Act of 2003.
32.1	Certification of Andrew T. Drechsler, Chief Financial Officer (Principal Financial and Accounting Officer) of Insmed Incorporated, pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes Oxley Act of 2003.

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32.2	Certification of Andrew T. Drechsler, Chief Financial Officer (Principal Financial and Accounting Officer) of Insmed Incorporated, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes Oxley Act of 2003.
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

+ The Securities and Exchange Commission has granted confidential treatment with respect to certain information in these exhibits. The confidential portions of these exhibits have been omitted and filed separately with the Securities and Exchange Commission.

* Confidential treatment has been requested for certain portions of this exhibit. The confidential portions of this exhibit have been omitted and filed separately with the Securities and Exchange Commission.

** Management contract or compensatory plan or arrangement of the Company required to be filed as an exhibit.