INSMED Inc
Form 10-K
February 23, 2017

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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, 2016

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, 2016, was $603.2 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 registrant's 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 1, 2017, there were 62,023,451 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 2017 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission no later than May 1, 2017 and to be delivered to shareholders in connection with the 2017 Annual Meeting of Shareholders, are herein incorporated by reference in Part III of this Form 10-K.

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INSMED INCORPORATED

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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 and ARIKAYCE 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 are based upon our current expectations and beliefs, and involve known and unknown risks, 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 following:

- *uncertainties in the research and development of our existing product candidates, including due to delays in patient enrollment or failure of our preclinical studies or clinical trials to satisfy pre-established endpoints;*
- *failure to develop, or to license for development, additional product candidates, including a failure to attract experienced third party collaborators;*
- *failure to obtain, or delays in obtaining, regulatory approval from the United States (US) Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other regulatory authorities for our product candidates or their delivery devices, including due to insufficient clinical data or selection of endpoints that are not satisfactory to regulators;*
- *failure of third parties on which we are dependent to conduct our clinical trials and to manufacture sufficient quantities of our product candidates for clinical or commercial needs;*
- *failure to comply with license agreements that are critical for our product development, including our license agreements with PARI Pharma GmbH (PARI) and AstraZeneca AB (AstraZeneca);*
- *lack of safety and efficacy of our product candidates;*
- *inaccuracies in our estimate of the size of the potential markets for our product candidates;*
- *failure to maintain regulatory approval for our product candidates, once received, due to a failure to satisfy post-approval regulatory requirements, such as the need for post-clinical trials;*
- *uncertainties in the rate and degree of market acceptance of product candidates, if approved;*
- *uncertainties in the timing, scope and rate of reimbursement for our product candidates;*
- *competitive developments affecting our product candidates;*
- *inaccurate estimates regarding our future capital requirements, including those necessary to fund milestone payments or royalties owed to third parties;*
- *inability to repay our existing indebtedness or to obtain additional financing when needed;*
- *failure to obtain, protect and enforce our patents and other intellectual property;*
- *inability to create an effective direct sales and marketing infrastructure or to partner with a third party that offers such an infrastructure for distribution of our product candidates;*
- *the cost and potential reputational damage resulting from litigation to which we are a party, including, without limitation, the class action lawsuit pending against us;*
- *failure to comply with the laws and regulations that impact our business;*
- *loss of key personnel; and*

- *changes in laws and regulations applicable to our business, including those related to pricing and reimbursement of our product candidates.*

We caution readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made. You should carefully read the factors discussed in Item 1A Risk Factors as well as those discussed in Item 7 Management's Discussion and Analysis of Financial Condition

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and Results of Operations and elsewhere throughout this Annual Report on Form 10-K for additional discussion of the risks and uncertainties that could cause our actual results to differ materially from those in our forward-looking statements. We disclaim any obligation, except as specifically required by law, to publicly update or revise any such statements to reflect any change in our expectations or in events after the date of this report.

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PART I

ITEM 1. BUSINESS

Business Overview

Insmed is a global biopharmaceutical company focused on the unmet needs of patients with rare diseases. Our lead product candidate is ARIKAYCE, or liposomal amikacin for inhalation (LAI), which is in late-stage development for adult patients with treatment refractory nontuberculous mycobacteria (NTM) lung disease caused by *Mycobacterium avium* complex (MAC), a rare and often chronic infection that is capable of causing irreversible lung damage and can be fatal. Our earlier clinical-stage pipeline includes INS1007 and INS1009. INS1007 is a novel oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1), an enzyme responsible for activating neutrophil serine proteases, which are implicated in the pathology of chronic inflammatory lung diseases, such as non-cystic fibrosis (non-CF) bronchiectasis. INS1009 is an inhaled nanoparticle formulation of a treprostinil prodrug that may offer a differentiated product profile for rare pulmonary disorders, including pulmonary arterial hypertension (PAH).

The table below summarizes the current status and anticipated milestones for our principal product candidates: ARIKAYCE, INS1007, and INS1009.

Product Candidate/Target Indications	Status	Next Expected Milestones
ARIKAYCE (LAI) for adult patients with treatment refractory NTM lung infections caused by MAC	We are advancing the CONVERT (or 212) study, a randomized, open-label global phase 3 clinical study of ARIKAYCE in adult patients with treatment refractory NTM lung disease caused by MAC. We have achieved our enrollment objective for the CONVERT study.	We expect to report top-line results for the Month 6 primary endpoint in the second half of 2017.
	The US Food and Drug Administration (FDA) has designated ARIKAYCE as an orphan drug, a breakthrough therapy, and a qualified infectious disease product (QIDP).	If the CONVERT study meets its primary endpoint, we intend to seek accelerated marketing approval for ARIKAYCE in the US. We intend to seek marketing approvals for ARIKAYCE in certain countries outside the US, when sufficient data are available. If approved, we expect ARIKAYCE would be the first inhaled antibiotic specifically indicated for the treatment of refractory NTM lung infections caused by MAC in North America, Europe, and Japan.
	The European Commission has granted an orphan designation for ARIKAYCE for the treatment of NTM lung disease.	
		If approved, we plan to commercialize ARIKAYCE in the US, certain countries in Europe, Japan and certain other countries.

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Product Candidate/Target Indications	Status	Next Expected Milestones
INS1007 (oral reversible inhibitor of dipeptidyl peptidase 1) for non-CF bronchiectasis	In October 2016, we entered into a license agreement with AstraZeneca for the exclusive global rights for the purpose of developing and commercializing AZD7986 (AZ License Agreement). We renamed the compound INS1007 and plan to pursue an initial indication of non-CF bronchiectasis.	We plan to submit an Investigational New Drug (IND) application with the FDA for non-CF bronchiectasis and subsequently commence a phase 2 clinical study of INS1007. The study is expected to begin in 2017.
	We are defining our regulatory strategies to potentially secure US and EU orphan drug designations and expedite the development and regulatory review of INS1007 through programs such as US fast track designation and breakthrough therapy.	
INS1009 (inhaled nanoparticle formulation of a treprostinil prodrug) for rare pulmonary disorders	The results of our phase 1 study of INS1009 were presented at the European Respiratory Society international congress in September 2016.	We believe INS1009 may offer a differentiated product profile for rare pulmonary disorders, including PAH, and we are currently evaluating our options to advance its development.
	The phase 1 study was a randomized, double-blind, placebo-controlled, single ascending dose study of INS1009 for inhalation to determine its safety, tolerability, and pharmacokinetics in healthy volunteers.	

Our earlier-stage pipeline includes preclinical compounds that we are evaluating in multiple rare diseases of unmet medical need, including methicillin-resistant staph aureus (MRSA) and NTM. To complement our internal research and development, we actively evaluate in-licensing and acquisition opportunities for a broad range of rare diseases.

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 company focused on the development of differentiated and innovative inhaled pharmaceuticals for the site-specific treatment of serious lung diseases.

Our Strategy

Our strategy focuses on the needs of patients with rare diseases. We are currently focused on the development and commercialization of ARIKAYCE. We are not aware of any inhaled products

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specifically indicated to treat refractory NTM lung disease in North America, Europe or Japan. While we believe that ARIKAYCE has the potential to treat a number of different bacterial infections, we are prioritizing securing US regulatory approval of ARIKAYCE for adult patients with refractory NTM lung disease caused by MAC. We are also advancing earlier-stage programs in other rare pulmonary disorders.

Our current priorities are as follows:

- Advancing the CONVERT study;
- Preparing a New Drug Application (NDA) for submission to the FDA for ARIKAYCE, which we plan to base on the primary endpoint of the CONVERT study;
- Ensuring our product supply chain will support the clinical development and, if approved, commercialization of ARIKAYCE;
- Preparing for potential commercialization of ARIKAYCE in the US, certain countries in Europe, Japan, and certain other countries;
- Developing the core value dossier to support the global reimbursement of ARIKAYCE;
- Supporting further research and lifecycle management strategies for ARIKAYCE;
- Filing an IND with the FDA and starting a phase 2 study of INS1007 in non-CF bronchiectasis;
- Generating preclinical findings from our earlier-stage program(s); and
- Expanding our rare disease pipeline through corporate development.

Product Pipeline

ARIKAYCE for patients with NTM lung disease

Our lead product candidate is ARIKAYCE, or LAI, a novel, once-daily liposomal formulation of amikacin that is in late-stage clinical development for adult patients with treatment refractory NTM lung disease caused by MAC, a rare and often chronic infection that is capable of causing irreversible lung damage and which can be fatal. Amikacin solution for parenteral administration is an established drug that has activity against a variety of NTM; however, its use is limited by the need to administer it intravenously and by toxicity to hearing, balance, and kidney function (Peloquin et al., 2004). Unlike intravenous amikacin, our advanced liposome technology uses charge-neutral liposomes to deliver amikacin directly to the lung where it is taken up by the lung macrophages where the NTM infection resides. This prolongs the release of amikacin in the lungs while minimizing systemic exposure thereby offering the potential for decreased systemic toxicities. ARIKAYCE's ability to deliver high levels of amikacin directly to the lung distinguishes it from intravenous amikacin. ARIKAYCE is administered once-daily, using a portable aerosol delivery system, via an optimized, investigational eFlow® Nebulizer System manufactured by PARI.

The FDA has designated ARIKAYCE as an orphan drug, a breakthrough therapy, and a QIDP for NTM lung disease. Orphan designation features seven years of post-approval market exclusivity, and QIDP features an additional five years of post-approval exclusivity. As a result, ARIKAYCE would have 12 years of post-approval marketing exclusivity in the US, if approved. A QIDP-designated product is eligible for fast track status and is often granted priority review status. A priority review designation for a drug means the FDA's goal is to take action on the NDA within six months following the 60-day filing date, as compared to 10 months of the 60-day filing date under a standard review.

The CONVERT study

ARIKAYCE is currently being evaluated in a phase 3 randomized, open-label clinical study taking place in North America, Europe, Australia, New Zealand and Asia that is designed to confirm the culture conversion results seen in our phase 2 clinical trial, which we expect will provide the basis

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for submitting an NDA to the FDA. Because the highest response to ARIKAYCE treatment in our phase 2 study was observed in the subgroup of non-CF patients with NTM lung infection caused by MAC, the CONVERT study is comprised of non-CF patients 18 years and older with an NTM lung infection caused by MAC that is refractory to a stable multi-drug regimen for at least six months, with the regimen either ongoing or interrupted within 12 months of screening. The CONVERT study excludes subjects whose susceptibility scores indicate that their MAC lung infection is resistant to amikacin. We achieved our enrollment objective for the CONVERT study in the fourth quarter of 2016.

After a screening period of approximately 10 weeks, eligible subjects were randomized 2:1 to once-daily ARIKAYCE plus a multi-drug regimen or a multi-drug regimen without ARIKAYCE. The first analysis, after the last patient has completed Month 6, will be based on the primary efficacy endpoint comparing the proportion of subjects who achieve culture conversion (three consecutive monthly negative sputum cultures) by Month 6 in the ARIKAYCE plus multi-drug regimen arm compared to the arm in which subjects receive a multi-drug regimen without ARIKAYCE. The study's key secondary endpoint in the first analysis includes the change from baseline in the six-minute walk test. A subsequent analysis will examine off-treatment assessments to evaluate the durability of the anti-mycobacterial effect on sputum culture at 3 months off all treatment. The study also includes a comprehensive pharmacokinetic sub-study in Japanese subjects in lieu of a separate local pharmacokinetic study in Japan.

At Month 8, after all sputum culture results are known up to and including Month 6, subjects will be assessed as converters (those achieving culture conversion by Month 6) or non-converters for the primary efficacy endpoint. All converters will continue on their randomized treatment regimen for an additional 12 months. All converters will return for off-treatment follow-up visits. A 12-month off-treatment study visit will be the last visit for the CONVERT study. All non-converters, as determined at the Month 8 visit, may be eligible to enter a separate 12-month, single-arm, open-label study (the 312 study). The primary objective of the 312 study is to evaluate the long-term safety and tolerability of ARIKAYCE in combination with a standard multi-drug regimen. The secondary endpoints of the 312 study include evaluating the proportion of subjects achieving culture conversion (three consecutive monthly negative sputum cultures) by Month 6 and the proportion of subjects achieving culture conversion by Month 12 (end of treatment).

The protocol for the CONVERT study incorporates feedback from the FDA and the EMA via its scientific advice working party process, as well as local health authorities in other countries, including Japan's Pharmaceuticals and Medical Devices Agency. If the CONVERT study meets the primary endpoint of culture conversion by Month 6, we believe we would be eligible to submit an NDA pursuant to 21 C.F.R. Part 314 Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses), which permits the FDA to approve a drug based on a surrogate or intermediate endpoint, provided the sponsor commits to study the drug further to verify and describe the confirmatory data of the drug's clinical benefit. We believe that efficacy data from the CONVERT study after Month 6 in combination with the durability data, if successful, will suffice to meet both the accelerated and confirmatory data requirements.

Phase 2 Study (112 Study)

Our completed phase 2 study, which is also known as the 112 study, was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of ARIKAYCE in adults with NTM lung disease due to MAC or *M. abscessus* that was refractory to guideline-based therapy. In October 2016, the results from the phase 2 study were published online in the *American Journal of Respiratory and Critical Care Medicine* (Olivier et al. 2016).

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The study included an 84-day double-blind phase in which subjects were randomized 1:1 either to ARIKAYCE once-daily plus a multi-drug regimen or to placebo once-daily plus a multi-drug regimen. After completing the 84-day double-blind phase, subjects had the option of continuing in an 84-day open-label phase during which all subjects received ARIKAYCE plus the same multi-drug regimen. The study also included 28-day and 12-month off-ARIKAYCE follow-up assessments. Eighty-nine (89) subjects were randomized and dosed in the study. Of the 80 subjects who completed the 84-day double-blind phase, 78 subjects entered the open-label phase and received ARIKAYCE plus the same multi-drug regimen for an additional 84 days. Seventy-six (76) percent (59/78) of subjects who entered the open-label phase of the study completed the open-label study.

The primary efficacy endpoint of the study was the change from baseline (Day 1) to the end of the double-blind phase of the trial (Day 84) in a semi-quantitative measurement of mycobacterial density on a seven-point scale. ARIKAYCE did not meet the pre-specified level for statistical significance although there was a positive trend (p=0.072) in favor of ARIKAYCE. The p-value for the key secondary endpoint of culture conversion to negative at Day 84 was 0.003, in favor of ARIKAYCE. A shorter time to first negative sputum culture was also observed with ARIKAYCE relative to placebo during the double-blind phase (p=0.013).

The microbiologic outcomes from the 112 study were also explored post hoc using a more stringent definition of culture conversion, which was defined as at least three consecutive monthly sputum samples that test negative for NTM, consistent with the definition of culture conversion in the guidelines and in clinical practice. Twenty-three (23) subjects achieved at least three consecutive negative monthly sputum samples by the 28-day follow-up assessment, of which four started to convert at baseline prior to administration of study drug. For the other 19 patients who achieved culture conversion, 17 achieved culture conversion after receiving ARIKAYCE (10 during the double-blind phase and seven after entering the open-label phase, of which six received ARIKAYCE for the first time in the open-label phase). Two patients achieved culture conversion while receiving placebo during the double-blind phase. The majority of subjects who achieved culture conversion (three consecutive negative monthly sputum samples) during the double-blind phase continued to have negative cultures through the open-label and follow-up phases.

At the end of the double-blind phase, the ARIKAYCE group improved from baseline in mean distance walked in the six-minute walk test. At the end of the open-label phase, patients in the ARIKAYCE group continued to improve in the mean distance walked in the six-minute walk test, while the patients who previously received placebo in the double-blind phase and subsequently received ARIKAYCE in the open-label phase demonstrated a reduced rate of decline from baseline.

Ninety (90) percent of patients in both treatment groups experienced at least one treatment-emergent adverse event with most events either mild or moderate in severity. During the double-blind phase a greater percentage of patients treated with ARIKAYCE experienced dysphonia, bronchiectasis exacerbation, cough, oropharyngeal pain, fatigue, chest discomfort, wheezing, and infective pulmonary exacerbation of cystic fibrosis. No clinically relevant changes were detected in laboratory values and vital signs.

Further research and lifecycle management for ARIKAYCE

We are exploring and supporting research and lifecycle management programs for ARIKAYCE beyond NTM lung infections caused by MAC. Lifecycle management initiatives are company-driven planning programs to help us reach more potential patients for ARIKAYCE, once sufficient data are generated and applicable regulatory bodies approve ARIKAYCE for these indications. These programs may include new clinical studies sponsored by us to develop data for such additional indications. We

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may also support investigator-initiated studies, which are clinical studies initiated and sponsored by physicians or research institutions with funding from us.

Marketing Authorization Application (MAA) for ARIKAYCE

In the fourth quarter of 2014, we filed an MAA with the EMA for ARIKAYCE as a treatment for NTM lung disease in adult patients and for cystic fibrosis (CF) patients with *Pseudomonas* lung infections. The filing was based on data from our phase 3 study in CF patients with *Pseudomonas* and our phase 2 study in patients with NTM. In February 2015, the EMA validated our MAA as complete for review. The EMA subsequently requested additional information with respect to the CF indication regarding the similarity of ARIKAYCE to another product that has an orphan designation for the same *Pseudomonas* indication. In the third quarter of 2015, the EMA adopted our request to withdraw the *Pseudomonas* indication from our MAA. In April 2016, we submitted our written responses to the EMA's 180-day list of outstanding issues (LOI). In May 2016, we participated in an oral explanation meeting with the EMA's Committee for Medicinal Products for Human Use (CHMP) for the NTM indication to address the LOI. After the oral explanation meeting, the CHMP concluded that the data submitted did not provide enough evidence to support an approval. In June 2016, we withdrew our MAA. We intend to resubmit our MAA when sufficient clinical data are available.

NTM Lung Disease Market Opportunity

NTM is a rare and serious disorder associated with increased morbidity and mortality. NTM currently includes over 185 species. MAC is the predominant pathogenic species in NTM pulmonary disease in the US, Japan and Europe, followed by *M. abscessus*, both of which we have studied in our development of ARIKAYCE. Our CONVERT trial is studying refractory NTM lung infections caused by MAC in adult patients. The prevalence of human disease attributable to NTM has increased over the past two decades, and it is an emerging public health concern worldwide.

A 2015 publication from co-authors from several US government departments projected approximately 180,000 cases of NTM lung disease in the US in 2014 (Strollo et al., 2015) (the Strollo publication) and is increasing at a rate of approximately 8% per year (1997-2007 research study). Previously, based on market research in 2012 and 2013 conducted by Clarity Pharma Research, we estimated that of patients who had a confirmed diagnosis of NTM lung disease, an estimated 10 to 30 percent were refractory to current treatments. In 2013, we engaged Clarity Pharma Research to perform a chart audit study of NTM lung disease in Europe and Japan, which estimated that there are approximately 20,000 cases of pulmonary disease attributable to NTM within the EU5, approximately 30,000 total cases in the 28 countries then-comprising the European Union (EU) and nearly 32,000 cases in Japan. Although population-based data on the epidemiology of NTM lung disease are limited, and determining the true prevalence and incidence of rare diseases can be challenging, studies worldwide have described an increasing prevalence of NTM lung disease.

Patients with NTM lung disease may experience a multitude of symptoms such as chronic cough, fever, weight loss, lack of appetite, night sweats, blood in the sputum, and fatigue, and frequently require lengthy, and repeat, hospital stays to manage their condition. In a burden of illness study that we conducted in the US with a major medical benefits provider, we concluded that patients with NTM lung infections are costly to healthcare plans and ATS/IDSA guideline-based treatment results in healthcare savings as opposed to suboptimal treatment. Other claims-based studies have shown the following:

- A 36.1% increase in the incidence of NTM lung infections between 2008 and 2013 in the US Medicare population of a national managed care health plan, with the greatest incidence increase (56.3%) observed in members 65 to 74 years of age. Following diagnosis with NTM

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lung infections, over 50% of members were still in the plan after six years (Abraham et al., 2015).

- Patients with NTM lung infections were using greater healthcare resources than their age and gender-matched controls in the period preceding their initial diagnosis. Ordering mycobacterial testing of sputum earlier may help in preventing a misdiagnosis or delaying a diagnosis (Holt et al., 2015).
- Higher resource utilization and costs for patients with NTM lung infections than their age and gender-matched controls both pre- and post-diagnosis. Patients who received treatment regimens conforming to the 2007 ATS/IDSA guidelines showed lower healthcare resource utilization and total medical costs than patients who received suboptimal treatment (Abraham et al., 2015).

Current ATS/IDSA guideline-based approaches involve multi-drug regimens that may cause severe side effects and treatment can last two years or more. We are not aware of any inhaled antibiotic treatments specifically indicated for the treatment of refractory NTM lung disease in North America, Europe or Japan.

INS1007

INS1007 is a small molecule, oral, reversible inhibitor of DPP1, which we in-licensed from AstraZeneca in October 2016. DPP1 is an enzyme responsible for activating neutrophil serine proteases in neutrophils when they are formed in the bone marrow. Neutrophils are the most common type of white blood cell and play an essential role in pathogen destruction and inflammatory mediation. Neutrophils, which play a key role in the pathologic inflammatory process, contain three neutrophil serine proteases, neutrophil elastase, proteinase 3, and cathepsin G, that have been implicated in a variety of inflammatory diseases. In chronic inflammatory lung diseases, neutrophils accumulate in the airways and result in excessive active neutrophil serine proteases that cause lung destruction and inflammation. INS1007 may decrease the damaging effects of inflammatory diseases, such as non-CF bronchiectasis, by inhibiting DPP1 and its activation of neutrophil serine proteases.

Non-CF bronchiectasis

Non-CF bronchiectasis is a rare, progressive pulmonary disorder in which the bronchi become permanently dilated due to chronic inflammation and infection. Symptoms include chronic cough, excessive sputum production, shortness of breath, and repeated respiratory infections, which can worsen the underlying condition. There is currently no cure for non-CF bronchiectasis. Bronchiectasis increases susceptibility to NTM lung disease, and up to 50 percent of patients with bronchiectasis may also have an active NTM lung infection.

Phase 1 study results

In a phase 1 study of healthy volunteers, INS1007 (previously AZD7986) was well tolerated and demonstrated inhibition of the activity of the neutrophil serine protease neutrophil elastase in a dose and concentration dependent manner. In preclinical studies, it was shown to reversibly inhibit DPP1 and the activation of neutrophil serine proteases within maturing neutrophils.

We plan to submit an IND application with the FDA for INS1007 in non-CF bronchiectasis, and after it becomes effective, to commence a phase 2 clinical study of INS1007 in that indication. We expect the study to begin in 2017. In addition, we are evaluating INS1007 in other potential indications.

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INS1009

INS1009 is an investigational sustained-release inhaled treprostinil prodrug nanoparticle formulation that has the potential to address certain of the current limitations of existing prostanoid therapies. We believe that INS1009 prolongs duration of effect and may provide PAH patients with greater consistency in pulmonary arterial pressure reduction over time. Current inhaled prostanoid therapies must be dosed four to nine times per day for the treatment of PAH. Reducing dose frequency has the potential to ease patient burden and improve compliance. Additionally, we believe that INS1009 may be associated with fewer side effects, including elevated heart rate, low blood pressure, and severity and/or frequency of cough, associated with high initial drug levels and local upper airway exposure when using current inhaled prostanoid therapies. We believe INS1009 may offer a differentiated product profile for rare pulmonary disorders, including PAH, and we are currently evaluating our options to advance its development.

Phase 1 study results

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 preclinical data, INS1009 could be eligible for an approval pathway 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 establish that the drug is safe and effective, but unlike a traditional NDA, the applicant may rely at least in part on studies not conducted by or for the applicant and for which the applicant does not have a right of reference. The ability to rely on existing third-party data to support safety and/or effectiveness can reduce the time and cost associated with traditional NDAs.

We have completed a phase 1 study of INS1009. The phase 1 study was a randomized, double-blind, placebo-controlled single ascending dose study of INS1009 for inhalation to determine its safety, tolerability, and pharmacokinetics in healthy volunteers. Twenty-four (24) subjects were enrolled and received INS1009 with cohorts of eight subjects receiving doses of 85 micrograms (mcg), 170 mcg, 340 mcg or placebo. Participants in the first cohort (8 patients) received a single dose of open label treprostinil (Tyvaso) at 54 mcg 24 hours prior to receiving INS1009 at 85 mcg. The 85 mcg dose of INS1009 provides an equivalent amount of treprostinil on a molar basis as the 54 mcg dose of Tyvaso. The peak serum concentration was approximately 90% lower for treprostinil after INS1009 administration compared with Tyvaso, which could indicate a reduced future adverse event (AE) profile. The pharmacokinetic characteristics also supported once- or twice-daily dosing. The longer half-life of treprostinil for INS1009 was likely due to a sustained pulmonary release. The AE profile was consistent with other inhaled prostanoids. These data were presented at the European Respiratory Society international congress in September 2016.

Research and Development

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. Expenses also include other internal operating expenses, the cost of manufacturing our drug candidates for clinical study (primarily related to activities at contract manufacturing organizations (CMOs) that manufacture ARIKAYCE for our use), the cost of conducting clinical studies (primarily related to activities at contract research organizations (CROs) that conduct and manage clinical trials on our behalf), and the cost of conducting preclinical and research activities. In addition, research and development expenses include payments to third parties for the license rights to products in development (prior to marketing approval). We incurred approximately $122.7 million, $74.3 million, and $56.3 million for research and development expenses in 2016, 2015 and 2014, respectively.

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Corporate Development

In October 2016, we exclusively licensed global rights to INS1007 from AstraZeneca and we plan to continue to develop, acquire, in license or co-promote complementary products that address rare diseases. We are focused broadly on rare disease therapeutics and prioritizing those areas that best align with our core competencies and current therapeutic focus in the area of rare pulmonary diseases.

Manufacturing

We do not have any in-house manufacturing capability other than for small-scale pre-clinical development programs, and depend on a small number of third-party manufacturers and suppliers for the manufacture of our product candidates for use in clinical trials. We plan to rely on third-party manufacturers and suppliers for the commercial manufacture and supply of any product candidates that we may commercialize. ARIKAYCE is manufactured by Therapure Biopharma Inc. (Therapure) in Canada at a 200 liter scale and by Ajinimoto Althea, Inc. (Althea) in the US at a 50 liter scale. For additional information about our agreements with Therapure and Althea, see *License and Other Agreements ARIKAYCE-Related Agreements*. We have also identified certain second source suppliers for our supply chain and plan to enter into supply and quality agreements with certain of these second source suppliers in preparation for commercialization of ARIKAYCE. In addition, we have entered into a commercialization agreement with PARI, the manufacturer of our drug delivery nebulizer for ARIKAYCE, to address our commercial supply needs (Commercialization Agreement).

We expect to enter into a commercial supply agreement with AstraZeneca related to certain short-term production needs for INS1007. We expect our future requirements for INS1007, beyond phase 2, will be manufactured by a CMO.

We currently produce INS1009 and plan to utilize third parties to manufacture INS1009 at a larger scale and to manufacture the nebulizer used to deliver the drug.

Intellectual Property

We own or license rights to more than 350 issued patents and pending patent applications in the US and in foreign countries, including more than 175 issued patents and pending patent applications related to ARIKAYCE. Our success depends in large 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 on inventions that are important to the development of our business in the US, Europe, Japan, Canada, and selected other foreign markets that we consider key for our product candidates. These international markets generally include Australia, 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 US 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,

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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, advisors, collaborators and other third-party partners 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.

ARIKAYCE Patents and Trade Secrets

Of the patents and applications related to ARIKAYCE, there are seven issued US patents that cover the ARIKAYCE composition and its use in treating NTM. Upon ARIKAYCE approval for the treatment of NTM, these patents may be eligible for listing in the FDA Orange Book. These patents and their expiration dates are as follows:

- US Patent No. 7,718,189 (expires June 6, 2025)
- US Patent No. 8,226,975 (expires August 15, 2028)
- US Patent No. 8,632,804 (expires December 5, 2026)
- US Patent No. 8,802,137 (expires April 8, 2024)
- US Patent No. 8,679,532 (expires December 5, 2026)
- US Patent No. 8,642,075 (expires December 5, 2026)
- US Patent No. 9,566,234 (expires January 18, 2034)

In addition, we own five pending US patent applications that cover the ARIKAYCE composition and its use in treating NTM. Upon ARIKAYCE approval for the treatment of refractory NTM lung disease caused by MAC, these patent applications, if issued as patents, may be eligible for listing in the FDA Orange Book. We also own a pending US application that covers methods for making ARIKAYCE.

Four patents have been granted by the European Patent Office (EPO) (European Patent Nos. 1581236, 1909759, 1962805 and 2363114) that cover ARIKAYCE and its use in treating NTM. In addition, we have five applications pending before the EPO that cover ARIKAYCE and its use in treating NTM lung disease. We also have a pending European application that covers methods of making ARIKAYCE. More than 40 patents have also been issued in other major foreign markets, e.g., Japan, China, Korea, Australia, and India, that cover ARIKAYCE and/or methods of using ARIKAYCE for treating various pulmonary disorders, including NTM lung disease. More than 60 foreign patent applications are pending that cover the ARIKAYCE composition and/or its use in treating various pulmonary disorders, including NTM lung disease. We anticipate that in the US, we will have potential patent coverage for ARIKAYCE and its use in treating NTM lung disease, through January 18, 2034, which does not include a potential six months of pediatric exclusivity.

Currently, our European Patent No. 2363114 is being opposed by Generics (UK) Ltd, a wholly-owned subsidiary of Mylan NV. The European Patent Office Opposition Division (EPOOD) issued a preliminary non-binding opinion regarding the opposition on January 2, 2017, and an oral hearing regarding the opposition has been scheduled for November 15, 2017. The preliminary non-binding opinion did not address every issue in the opposition, but was favorable to us regarding the issues that were addressed. European Patent No. 1909759, owned by us, was previously opposed by Generics (UK) Ltd. An oral hearing was held on October 19, 2015 during which, we submitted amended claims. The EPOOD maintained the patent as amended. This decision is currently under appeal by Generics (UK) Ltd.

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Through our agreements with PARI, we have license rights to US and foreign patents and applications that cover the eFlow Nebulizer System medical device through January 18, 2034. We have rights to use the nebulizers in clinical trials, and we have entered into a commercial supply agreement with PARI.

The basic terms of utility patents issued in the US are the longer of 17 years from the issue date or 20 years from the earliest effective filing date, if the patent was in force on or was issued from a patent application that 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. All ARIKAYCE patent applications have earliest effective filing dates falling after June 8, 1995. The basic term of foreign utility patents may vary in accordance with provisions of applicable local law, but is typically 20 years from the earliest effective filing date.

INS1007 Patents

Through our agreement with AstraZeneca, we have licensed U.S. Patent No. 9,522,894, which has claims directed to INS1007 and expires January 21, 2035 (not taking into account any potential patent term extension). Counterpart patent applications are pending throughout the world and a continuation application is pending in the US.

INS1009 Patents

We own US Patent No. 9,255,064 (expires October 24, 2034), which is the first patent to issue with claims covering hexadecyl-treprostinil, the treprostinil component of INS1009. Other treprostinil prodrugs are also claimed and described in the patent. We also own US Patent No. 9,469,600, which has claims directed to INS1009 and other treprostinil prodrug nanoparticle formulations and expires October 24, 2034. Counterpart patent applications to US Patent Nos. 9,255,064 and 9,469,600 are pending in Europe, Japan and other foreign jurisdictions.

We own pending patent applications that if granted, would cover methods for using treprostinil prodrugs and nanoparticle formulations comprising the same, including INS1009 in treating patients with PAH and other diseases, as well as methods for manufacturing such treprostinil prodrugs and nanoparticle formulations.

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 and ARIKAYCE. At present, we have received either a registration or a notice of allowance for the INSMED and ARIKAYCE marks from the US Patent and Trademark Office. We have also received foreign notices of allowance or registrations for the INSMED and ARIKAYCE marks, among others. The EMA has indicated it has no objection to our use of the name ARIKAYCE, and the FDA has conditionally approved our use of the name ARIKAYCE as the proposed trade name for our LAI 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.

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License and Other Agreements

ARIKAYCE-related Agreements

We currently rely, and will continue to rely, on agreements with a number of third parties in connection with the development and manufacture of ARIKAYCE.

PARI Pharma GmbH

We have a licensing agreement with PARI for use of the optimized eFlow Nebulizer System for delivery of ARIKAYCE in treating patients with NTM lung infections, CF and bronchiectasis. Under the licensing agreement, we have rights under several US and foreign issued patents, and patent applications involving improvements to the optimized eFlow Nebulizer System, to exploit such system with ARIKAYCE for the treatment of such indications, but we cannot manufacture such nebulizers except as permitted under our Commercialization Agreement with PARI. We currently have rights to use the nebulizers in clinical trials. The eFlow Nebulizer System is labeled as investigational for use in our clinical trials in the US, Japan, Canada and Australia and must receive regulatory approval before we can market ARIKAYCE; the eFlow Nebulizer System has been approved for use in the EU.

We have certain obligations under this licensing agreement in relation to specified licensed indications. With respect to CF, we are obligated to use commercially reasonable efforts to develop, obtain regulatory and reimbursement approval, market and sell ARIKAYCE in two or more major European countries. With respect to NTM, CF and bronchiectasis, we have specific obligations to use commercially reasonable efforts to achieve certain developmental and regulatory milestones by set deadlines. Additionally, for NTM, we are obligated to use commercially reasonable efforts to achieve certain commercial milestones in the US, Europe and Canada. The consequences of our failing to use commercially reasonable efforts to achieve these milestones are context-specific, but include ending PARI's non-compete obligation, making the license non-exclusive and terminating the license, in each case with respect to the applicable 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.

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 obligations. 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.

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In July 2014, we entered into the Commercialization Agreement with PARI for the manufacture and supply of eFlow nebulizer systems and related accessories (the Device) as optimized for use with our proprietary LAI. The Commercialization Agreement envisages that PARI will undertake the manufacturing of the Device except in the case of certain defined supply failures, when we will have the right to make the Device and have it made by third parties (but not certain third parties deemed under the Commercialization Agreement to compete with PARI). The Commercialization Agreement has an initial term of fifteen years from the first commercial sale of ARIKAYCE pursuant to the licensing agreement. The term of the Commercialization 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.

Althea

In September 2015, we entered into a Commercial Fill/Finish Services Agreement (the Fill/Finish Agreement) with Althea to produce, on a non-exclusive basis, ARIKAYCE in finished dosage form at a 50-liter scale. We are obligated to pay a minimum of $2.7 million for the batches of ARIKAYCE produced by Althea each calendar year during the term of the Fill/Finish Agreement. The Fill/Finish Agreement became effective as of January 1, 2015, and had an initial term that was to end on December 31, 2017. In 2016, we signed an extension of the Fill/Finish Agreement through December 31, 2019, and it may be extended for additional two-year periods upon mutual written agreement of us and Althea at least one year prior to the expiration of its then-current term.

Either we or Althea may terminate the Fill/Finish Agreement upon the occurrence of certain events, including (i) material breach of the Fill/Finish Agreement by either party, provided such breach is not cured within 30 days after receipt by the breaching party of written notice of the breach or (ii) insolvency or bankruptcy of the other party. In addition, we may terminate the Fill/Finish Agreement without cause with 12 months' prior written notice to Althea, and Althea may terminate the Agreement without cause with 24 months' prior written notice to us.

Therapure

In February 2014, we entered into a Contract Manufacturing Agreement with Therapure for the manufacture of ARIKAYCE at a 200-liter scale. Pursuant to the agreement, we collaborated with Therapure to construct a production area for the manufacture of ARIKAYCE in Therapure's existing manufacturing facility in Mississauga, Ontario, Canada. Therapure manufactures 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. Under the agreement, we are obligated to pay certain minimum amounts for the batches of ARIKAYCE produced each calendar year. 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, and (ii) the default or bankruptcy of the other party. In addition, we may terminate the agreement for any reason upon no fewer than 180 days' advance notice.

SynteractHCR, Inc. (Synteract)

We entered into a services agreement with Synteract pursuant to which we retained Synteract to perform implementation and management services in connection with the 212 study. We may

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terminate the services agreement or any work order for any reason and without cause with 30 days' written notice. Either party may terminate the agreement in the event of a material breach or, bankruptcy petition by the other party or, if any approval from a regulatory authority is revoked, suspended or expires without renewal. We anticipate that aggregate costs relating to all work orders for the 212 study will be approximately $45 million over the period of the study. In April 2015, we entered into a work order with Synteract to perform implementation and management services for the 312 study. We anticipate that aggregate costs relating to all work orders for the 312 study will be approximately $25 million over the period of the study.

Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT)

In 2004 and 2009, we entered into research funding agreements with 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 five years of the drug commercialization, we would owe an additional payment of $3.9 million. Under the 2009 agreement, in the event we terminate development of ARIKAYCE for CF prior to first commercial sale of a product containing ARIKAYCE for a period of 360 continuous days, and such termination is not for reasons outside of our reasonable control, then at CFFT's election and within 180 days of such termination, CFFT (1) may elect to develop ARIKAYCE and (2) will have the right to receive from us an exclusive (subject to certain exceptions), royalty-free, sub-licensable license to use, develop, sell and commercialize a product containing ARIKAYCE in the treatment of certain infections in CF patients or pulmonary disease.

INS1007-related License Agreement

In October 2016, we entered into the AZ License Agreement, pursuant to which AstraZeneca granted us exclusive global rights for the purpose of developing and commercializing AZD7986 (renamed INS1007). In consideration of the licenses and other rights granted by AstraZeneca, we made an upfront payment of $30.0 million in late October 2016. We are obligated to make a series of contingent milestone payments to AstraZeneca totaling up to an additional $85.0 million upon the achievement of clinical development and regulatory filing milestones. If we elect to develop INS1007 for a second indication, we will be obligated to make an additional series of contingent milestone payments totaling up to $42.5 million. We are not obligated to make any additional milestone payments for any additional indications. In addition, we have agreed to pay AstraZeneca tiered royalties ranging from a high single-digit to mid-teen on net sales of any approved product based on INS1007 and one additional payment of $35.0 million upon the first achievement of $1 billion in annual net sales. The AZ License Agreement provides AstraZeneca with the option to negotiate a future agreement with us for commercialization of INS1007 in chronic obstructive pulmonary disease or asthma. If we fail to comply with our obligations under our agreements with AstraZeneca (including, among other things, if we fail to use commercially reasonable efforts to develop and commercialize a product based on INS1007, or we are subject to a bankruptcy or insolvency), AstraZeneca would have the right to terminate the license.

INS1009-related Agreement

In November 2015, we entered into an agreement with Respironics Inc., a division of Philips (Respironics), for the clinical supply of nebulizers to be used in the development of INS1009 for PAH. The agreement calls for payments to Respironics upon the achievement of certain clinical milestones

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relating to the development of INS1009, aggregating to $7.6 million. In addition, we will be required to pay a royalty on net sales of the product, if any.

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. Additionally, there currently are, and in the future there may be, already-approved products for certain of the indications for which we are developing, or in the future may choose to develop, our product candidates. For instance, PAH is a competitive indication with established products, including other formulations of treprostinil.

NTM lung disease competitive overview

In the NTM lung disease market, our major competitors include pharmaceutical and biotechnology companies that have approved therapies or therapies in development for the treatment of chronic lung infections. While some companies have expressed interest in studying their products for NTM, we are not aware of any companies that are currently conducting clinical trials for the treatment of refractory NTM lung disease or of any approved inhaled therapies specifically indicated for refractory NTM lung infections in North America, Europe or Japan, but, as previously described, there is an ATS/IDSA-recommended treatment regimen that is utilized.

Government Regulation

Orphan Drug 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 (for the purposes of the ODA, "rare" is generally defined as a disease or condition for which the drug is intended affects fewer than 200,000 people in the US) if it meets certain criteria specified by the ODA and FDA. After the FDA grants orphan drug designation, the drug and the specific intended use(s) for which it has obtained designation are listed by the FDA in a publicly-accessible database. The FDA has designated ARIKAYCE as an orphan drug for treatment of (i) infections caused by NTM, (ii) bronchiectasis in patients with *Pseudomonas* aeruginosa or other susceptible microbial pathogens and (iii) bronchopulmonary *Pseudomonas* aeruginosa infections in CF patients.

Orphan drug designation qualifies the sponsor for various development incentives of the ODA, including tax credits for qualified clinical testing, and a waiver of the NDA user fee (unless the application seeks approval for an indication not included in the orphan drug designation). Orphan drug designation also affords the company a period of marketing exclusivity upon approval of the drug. Specifically, the first NDA applicant with an FDA orphan drug designation for a particular active

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moiety 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 drug and indication. A product that has several separate orphan designations may have several separate market exclusivities. 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, and it does not alter the timing or scope of the regulatory review and approval process; the sponsor must still submit evidence from clinical and non-clinical studies sufficient to demonstrate the safety and effectiveness of the drug.

European Union

The European Commission grants orphan drug designation to promote the development of drugs or biologics (1) for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the EU, or (2) for life threatening, seriously debilitating or serious and chronic condition in the EU where, without incentives, sales of the drug in the European Economic Area (the European Union plus Iceland, Lichtenstein, and Norway) (EEA) are unlikely to be sufficient to justify its development. Orphan drug designation is available either if no other satisfactory method of diagnosing, preventing or treating the condition is approved in the EEA or if such a method does exist but the proposed orphan drug will be of significant benefit to patients. The European Commission has granted an orphan designation for ARIKAYCE for the treatment of NTM lung disease.

If a drug with 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 exclusivity. Orphan exclusivity means that the EMA or national medicines agency may not accept another application for authorization, or grant an authorization, for a same or similar drug for the same therapeutic indication. Competitors may receive such a marketing authorization despite orphan exclusivity, provided that they demonstrate that the existing orphan product is not supplied in sufficient quantities or that the 'second' drug or biologic is clinically superior to the existing orphan product. The 'second' drug may but need not have an orphan designation as well. The period of orphan exclusivity is ten years, which can be extended by two years where an agreed pediatric investigation plan has been implemented. The exclusivity period may also 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. 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 may have several separate market exclusivities.

Orphan drug designation also provides opportunities for free protocol assistance and fee reductions for access to the centralized regulatory procedure or fee exemptions for companies with a small and medium enterprises status. In addition, Member States may provide national benefits to orphan drugs, such as early access to the reimbursement procedure or exemption from any turnover tax imposed on pharmaceutical companies.

The orphan designation may be applied for at any time during the development of the drug but before the application for marketing authorization. At the time of marketing authorization, the criteria for orphan designation are examined again, and the Commission decides on the maintenance of the orphan designation. The non-maintenance of the orphan designation means that the drug loses its orphan status and thus no longer benefits from orphan exclusivity, fee reductions or exemptions, and national benefits.

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Drug Approval

United States

In the US, pharmaceutical products are subject to extensive regulation by the FDA and other government bodies. The 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 product development, approval, or after approval may subject a company to a variety of administrative or judicial sanctions, such as imposition of clinical holds, FDA refusal to file or approve 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. The description below summarizes the current approval process in the US for our product candidates.

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, formulation and toxicity, and 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 the FDA's good laboratory practices (GLP) regulations and the US Department of Agriculture's regulations implementing the 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 application. 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 all applicable federal regulations and guidance, including those pertaining to good clinical practice (GCP) standards that are meant to protect the rights, safety, and welfare of human subjects and to define the roles of clinical trial sponsors, investigators, and monitors as well as (ii) 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 of a new drug in the US (whether in patients or healthy volunteers) must be included as a submission to the IND, and the FDA must be notified of subsequent protocol amendments, including new protocols. In addition, the protocol must be reviewed and approved by an institutional review board (IRB), and all study subjects must provide informed consent. Typically, before any clinical trial, each institution participating in the trial will require review of the protocol before the trial commences at that institution. 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 certain adverse events.

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A study sponsor might choose to discontinue a clinical trial or a clinical development program for a variety of reasons. The FDA may impose a temporary or permanent clinical hold, or other sanctions, if it believes that the clinical trial either is not being conducted in accordance with the 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 pre-approval phases, but the phases may overlap or be combined. In Phase 1, short term (typically less than a few months) testing is conducted in a small group of subjects (typically 20-100), who may be patients with the target disease or condition or healthy volunteers, to evaluate its safety, determine a safe dosage range, and identify side effects. In Phase 2, the drug is given to a larger group of subjects (typically up to several hundred) with the target condition to further evaluate its safety and gather preliminary evidence of efficacy. Phase 3 studies typically last between several months and two years. In Phase 3, the drug is given to a large group of subjects with the target disease or condition (typically several hundred to several thousand), often at multiple geographical sites, to confirm its effectiveness, monitor side effects, and collect data to support drug approval. Only a small percentage of investigational drugs complete all three phases of development and obtain marketing approval.

NDA

After completion of the required clinical testing, an NDA can be 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 is a large submission that must include, among other things, 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 application also includes representative samples, copies of all drug product labeling, patent information, and a financial certification or disclosure statement. 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 annual product and establishment user fees also apply, which typically increase annually.

The FDA has 60 days from its receipt of an NDA to determine whether the application is 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 a substantive review. 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 outside 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 an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will typically 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 (cGMP) is satisfactory and the NDA contains data that provide substantial evidence, generally consisting of adequate and well-controlled clinical investigations, that the drug is safe and effective in the indication(s) studied. The FDA also reviews the proposed labeling submitted with the NDA and typically requires changes in the labeling text.

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

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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. An approval letter, which may specify post approval requirements, authorizes commercial marketing of the drug for the approved indication or indications and the other conditions of use set out in the approved prescribing information. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing. Under priority review status, the FDA has 180 days from the date of an NDA filing to issue either an approval letter or a complete response letter, unless the review period is adjusted by mutual agreement between the FDA and the applicant or as a result of the applicant submitting a major amendment. In practice, however, the performance goals established pursuant to the Prescription Drug User Fee Act have effectively extended the initial review cycle beyond 180 days. The FDA's current performance goals call for the FDA to complete review of 90 percent of standard (non-priority) NDAs within 10 months of filing and within six months of filing for priority NDAs (two additional months are added to standard and priority NDAs for a new molecular entity (NME) after the FDA receives an application for the agency to determine whether the application may be filed).

As a condition of NDA approval, the FDA may require substantial post-approval testing, known as phase 4 studies, to be conducted in order to gather additional information on the drug's effect in various populations and any side effects associated with long-term use. Beyond routine post marketing safety surveillance, the FDA may require specific additional 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. As a condition of approval, or after approval, the FDA also may require submission of a risk evaluation and mitigation strategy (REMS) to mitigate any identified or suspected serious risks. The REMS may 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. Further post-approval requirements are discussed below.

Expedited Review and Approval of Eligible Drugs

Accelerated approval regulations allow certain drugs for serious or life-threatening conditions to be approved on the basis of surrogate endpoints (i.e., clinical endpoints other than survival or irreversible morbidity) or intermediate clinical endpoints, which can substantially reduce time to approval. 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.

As a condition of approval, the FDA may require certain adequate and well-controlled post-marketing clinical studies to verify and describe clinical benefit of the product, and may impose restrictions on distribution to assure safe use. Post marketing studies would usually be required to be studies already underway at the time of the accelerated approval. In addition, promotional materials for an accelerated approval drug to be used in the first 120 days post-approval must be submitted to the FDA prior to approval, and materials to be used after that 120-day period must be submitted 30 days prior to first use. 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 under streamlined procedures in accordance with the agency's regulations. The agency may also withdraw approval of a drug if, among other things, the promotional

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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.

The FDA also has various programs fast track designation, priority review, and breakthrough designation that are intended to expedite or streamline 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. The programs each have different eligibility criteria and provide different benefits, and can be applied either alone or in combination depending on an applicant's circumstances. Fast track designation applies to a drug that is intended to treat a serious condition and for which nonclinical or clinical data demonstrate the potential to address unmet medical need. It should be requested at the time of IND submission or ideally no later than the pre-NDA meeting. The FDA must respond to requests for fast track designation within 60 days of receipt of the request. If granted, the applicant is eligible for actions to expedite development and review, such as frequent interaction with the review team, as well as for rolling review, meaning that the applicant may submit sections of the application as they are available. The timing of FDA's review of these sections depends on a number of factors, and the review clock does not start running until the agency has received a complete NDA submission. The FDA may withdraw fast track designation if the agency determines that the designation is no longer supported by data emerging in the clinical trial process.

Priority review applies to an application (both original and efficacy supplement) for a drug that treats a serious condition and that, if approved, would provide a significant improvement in safety or effectiveness. It also applies to any supplement that proposes a labeling change pursuant to a report on a pediatric study. A request for priority review is submitted at the time of NDA or supplemental NDA submission. The FDA must respond within 60 days of receipt of the request. If granted, the review time is shortened from the standard 10 months to 6 months, with two additional months in the case of a NME.

Breakthrough therapy designation applies to a drug that is intended to treat a serious condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. It can be requested with the IND submission and ideally no later than the end-of-phase 2 meeting. The FDA must respond within 60 days of receipt of the request. If granted, the applicant receives intensive guidance on efficient drug development, intensive involvement of senior managers and experienced review and regulatory health project management staff in a proactive, collaborative, cross-disciplinary review, rolling review, and other actions to expedite review. Designation may be rescinded if the product no longer meets the criteria for breakthrough therapy designation. ARIKAYCE has been designated as a breakthrough therapy.

Drugs that are designated as QIDPs are eligible for priority review and fast track designation, and well as market exclusivity. A product is eligible if it is an antibacterial or anti-fungal drug for human use that is intended to treat serious or life-threatening infections, including: those caused by an anti-bacterial or anti-fungal resistant pathogen, including novel or emerging infectious pathogens; or caused by qualifying pathogens listed by the FDA. A drug sponsor may request that the FDA designate its product as a QIDP at any time prior to NDA submission. The FDA must make a QIDP determination within 60 days of receiving the designation request. ARIKAYCE has been designated as a QIDP for NTM lung disease.

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Exclusivities

After NDA approval, owners of relevant drug patents may apply for up to a five-year patent extension on a single patent. 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 the 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 an NDA has not been submitted.

A variety of non-patent exclusivity periods are available under the FDCA that can delay the submission or approval of certain applications for competing products.

A five-year period of non-patent exclusivity within the US is granted to the first applicant to gain approval of an NDA for a new chemical entity (NCE). An NCE is a drug that contains no active moiety (the molecule or ion responsible for the action of the drug substance) that has been approved by the FDA in any other application submitted under section 505(b) of the Act. During the exclusivity period for a NCE, 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 (i.e., relies on FDA prior approval of) the NCE 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 with respect to a patent listed with the FDA for the reference NDA.

A three-year period of non-patent exclusivity is granted for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the sponsor that were essential to 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, which means that the FDA may approve applications for other versions of the original, unmodified drug product. Where this form of exclusivity applies, it prevents FDA approval of an ANDA or 505(b)(2) NDA subject to the exclusivity for the three-year period; however, the FDA may accept and review ANDAs or 505(b)(2) NDAs during the three-year period.

These exclusivities also do not preclude FDA approval of a 505(b)(1) application for a duplicate version of the drug during the period of exclusivity, provided that the applicant conducts or obtains a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Products with QIDP designation may receive a five-year extension of other non-patent exclusivities for which the drug is also eligible. The exclusivity does not prevent the FDA from approving a subsequent application for a change to the QIDP-designated drug that results in a new indication, route of administration, dosing, schedule, dosage form, delivery system, delivery device or strength. For example, an approved product with orphan designation and QIDP designation, like ARIKAYCE, would have 12 years of marketing exclusivity.

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Medical Device Regulation

Medical devices, such as the eFlow Nebulizer System, may receive marketing authorization from the FDA as stand-alone devices, or in some cases, may receive marketing authorization as part of a combination product. In either case, the ultimate product will need to satisfy FDA requirements. The primary pathways for marketing authorization for devices in the US are 510(k) clearance or premarket approval (PMA).

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.

The FDCA permits medical devices intended for investigational use to be shipped to clinical sites if such devices comply with prescribed procedures and conditions. Devices intended for investigational use may be exempted from premarket notification and premarket approval requirements when shipped for use in clinical trials, but they must bear a label indicating that they are for investigational use. This labeling may not represent that the device is safe or effective for the purposes for which it is being investigated.

Combination Products

A combination product is a product comprising two or more regulated components (e.g., a drug and device) that are combined into a single product, co-packaged, or sold separately but intended for co-administration, as evidenced by the labeling for the products. A drug that is administered using a nebulizer, such as ARIKAYCE or INS1009, is an example of a combination drug/device product.

The FDA is divided into various Centers, which each have authority over a specific type of product. NDAs are reviewed by personnel within the Center for Drug Evaluation and Research, while device applications and premarket notifications are reviewed by the Center for Devices and Radiological Health. When reviewing a drug/device combination product, the FDA must assign a lead Center to review the product, based on the combination product's primary mode of action (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 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. In addition, the Office of Combination Products (OCP) oversees the alignment of feedback regarding reviews involving multiple Centers and ensures that each Center completes its review and provides results to the lead Center in a timely manner.

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. Depending on the type of combination product, approval or clearance could be obtained through submission of a single marketing application or through separate applications for the individual constituent parts (i.e., an NDA for the drug and a premarket notification for the device). The FDCA directs the FDA to conduct a review of a combination product under a single marketing application whenever appropriate. This application is submitted to the Center selected to be the lead evaluator. The agency has the discretion to require

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separate applications to more than one Center, and applicants may choose to submit separate applications for constituent parts of a combination (unless the FDA determines one application is necessary). One reason to submit multiple applications 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 application is generally reviewed by the Center with authority over each application type. For combination products that contain an approved constituent part (such as a drug-device combination product in which the device has previously received clearance), the FDA may require that the application(s) include only such information as is necessary to meet the standard for clearance or approval, taking into account any prior finding of safety or effectiveness for the approved constituent part.

Like their constituent products e.g., 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 and promotion requirements and restrictions.

Disclosure of Clinical Trial Information

Under US and certain foreign laws intended to improve clinical trial transparency, sponsors of clinical trials may be required to register and disclose certain information about their clinical trials. This can include information related to the investigational drug, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial. This information is then made publicly available. Under a recently revised regulation in the US, sponsors are obligated to disclose the results of these trials after completion (prior to the new rulemaking, disclosure of results was only required if the product or new indication was approved by the FDA). In the US, disclosure of the results of these trials can be delayed for up to two years if the sponsor is seeking approval of the product or a new indication. Competitors may use this publicly-available information to gain knowledge regarding the progress of development programs.

Other Post-approval Regulatory Requirements

Once an NDA is approved, a product will be subject to certain post-approval requirements, including those relating to advertising, promotion, adverse event reporting, recordkeeping, and cGMP, as well as registration, listing, and inspection. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

The FDA regulates the content and format of prescription drug labeling, advertising, and promotion, including direct-to-consumer advertising and promotional Internet communications. FDA also establishes parameters for permissible non-promotional communications between industry and the medical community, including industry-supported scientific and educational activities. 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 or otherwise not to have met applicable promotion rules may be subject to significant liability under both the FDCA and other statutes, including the False Claims Act.

Manufacturers are subject to requirements for adverse event reporting and submission of periodic reports following FDA approval of an NDA.

All aspects of pharmaceutical manufacture must conform to cGMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA

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during which the FDA inspects manufacturing facilities to assess compliance with cGMPs. 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 areas of production and quality control to maintain compliance with cGMPs.

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, product formulation, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement, in some cases before the change may be implemented. An 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.

As previously mentioned, the FDA also may require phase 4 studies and may require a REMS, which could restrict the distribution or use of the product.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act (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.

European Union

Marketing Authorization Application

To obtain approval of a drug under the EU regulatory system, an application for a marketing authorization may be submitted under a centralized, a decentralized or a national procedure. The centralized procedure, which is compulsory for medicines produced by certain biotechnological processes or for orphan drugs, provides for the grant of a single marketing authorization that is valid for all EU member states, which grants the same rights and obligations in each member state as a national marketing authorization. As a general rule, only one marketing authorization may be granted for drugs approved through the centralized procedure and the marketing authorization is also relevant for the EEA countries.

Under the centralized procedure, the 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 designated by the CHMP, it adopts a list of questions, which are sent to the applicant together with the CHMP's overall conclusions. 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, revise the assessment report as necessary and may prepare a list of outstanding issues. The revised assessment report and list of outstanding issues are sent to the applicant together with the CHMP's recommendation by day 180 of the procedure. Applicants then have one month to respond to the CHMP (and can request a one or two-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

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whether to grant the marketing authorization. After the adoption of the CHMP opinion, a decision 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 European Commission adopts a decision within 15 days of the end of the consultation procedure.

Accelerated Procedure, Conditional Approval and Approval Under Exceptional Circumstances

Various programs, including accelerated procedure, 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 which are of major interest from the point of view of public health, 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 from 210 to 150 days.

Furthermore, for certain categories of medicinal products, marketing authorizations may be granted on the basis of less complete data than is normally required in order to meet unmet medical needs of patients or in the interest of public health. In such cases, the company may request, or the CHMP may recommend, the granting of a marketing authorization, subject to certain specific obligations; such marketing authorization may be conditional or under exceptional circumstances. The timelines for the centralized procedure described above also apply with respect to applications for a conditional marketing authorization or marketing authorization under exceptional circumstances.

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) the applicant will likely 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 granting of conditional marketing authorization depends on the applicant's ability to fulfill the conditions imposed within the agreed upon deadline. They are subject to "conditions", i.e. the holder is required to complete ongoing studies or to conduct new studies with a view to confirming that the benefit-risk balance is positive or to fulfill specific obligations in relation to pharmacovigilance. 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, they are 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 in order to ensure that the risk-benefit balance remains positive.

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Exclusivities

If an approved drug contains a new active substance, it is protected by data exclusivity for eight years from the notification of the Commission decision granting the marketing authorization and then by marketing protection for an additional two or three years. Overall, the drug is protected for ten or eleven years against generic competition, and no additional exclusivity protection is granted for any new development of the active substance it contains.

During the eight-year period of data exclusivity, competitors may not refer to the marketing authorization dossier of the approved drug for regulatory purposes. During the period of marketing protection, competitors may not market their generic drugs. The period of marketing protection is normally two years but may become three years if, during the eight-year data exclusivity period, a new therapeutic indication is approved that is considered as bringing a significant clinical benefit over existing therapies.

Medical Devices Regulations

In the EU, the marketing of medical devices is not subject to a prior approval by a health authority, but, depending on the class of device, may require prior review by a Notified Body. Notified Bodies are technical review bodies that are accredited and supervised by national health authorities. They conduct conformity assessment procedures of, among others, medical devices.

Medical devices are generally governed by Directive 93/42/EEC on Medical Devices that harmonizes the conditions for placing medical devices on the European market. This Directive however does not regulate certain important marketing aspects, such as advertising or pricing and reimbursement, which remain governed by national law.

Directive 93/42 requires medical devices to meet the essential requirements which are enumerated in the annexes to the Directive. Compliance with those requirements is demonstrated by the CE mark as the manufacturer may only affix the CE mark if it may declare conformity with the essential requirement for each medical device that is marketed. Directive 93/42 provides recourse to harmonized European standards in order to facilitate compliance with the essential requirements. Harmonized standards provide a presumption of conformity with the essential requirements.

Directive 93/42 institutes several conformity assessment procedures. The relevant conformity assessment procedure depends on the type of medical device and the risks involved. Devices are divided in four groups: Class I, Class IIa, Class IIb, and Class III. Class I devices present the lowest level of risk so that, for most of these devices the manufacturer can self-certify the product and need not rely on certification by a Notified Body. For the other classes, a Notified Body must review the manufacturer's procedures and/or the product. Every device is initially classified by the manufacturer. However, the Notified Body may dispute the classification and assert that the device should be included in a class requiring stricter conformity assessment procedures. Specific rules apply to custom-made medical devices, medical devices that are used in clinical trials, and medical devices that incorporate a medicinal ingredient.

For classes of devices other than Class I, a manufacturer must have a Notified Body test and certify conformity of its design and production procedures or its products with the essential requirements of Directive 93/42. Certification takes the form of a certificate of conformity issued by the Notified Body, which is valid throughout the European Union. Upon certification by the Notified Body, the manufacturer affixes the CE mark to the medical device, which allows the product to move freely within the EU and thus prevents EU Member States from restricting sales and marketing of the

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devices, unless such measure is justified on the basis of evidence of non-compliance. Ultimately, the manufacturer is responsible for the conformity of the device with the essential requirements and for the affixing of the CE mark. The eFlow Nebulizer System is CE marked by PARI in the EU.

Manufacturers of medical devices are subject to materiovigilance obligations that require reporting of incidents or near incidents related to the use of a medical device, which incidents may demonstrate the need for corrective action by the manufacturer. In addition, Notified Bodies regularly re-assess the conformity of a medical device to the essential requirements of Directive 93/42 and may from time to time audit the manufacturer and may, where needed, suspend or withdraw the manufacturer's certificate of conformity.

Japan

The Minister of Health, Labor 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, Labor 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 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 product fail to conform to the standards stipulated in the ordinances promulgated by the Ministry of Health, Labor 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 take 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.

Pediatric Information

United States

Under the Pediatric Research Equity Act of 2003 (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 the FDA's "written request" for pediatric research. Sponsors may seek to negotiate the terms of a written request during drug development. While the

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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.

European Union

In the EU, 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, subject to one or more waivers or deferrals. On 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 the 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.

Regulation Outside the US, Europe and Japan

In addition to regulations in the US, Europe and Japan, we will be subject to a variety of regulations in other jurisdictions governing clinical studies of our candidate products, including medical devices. Regardless of whether we obtain FDA approval for a product candidate, we must obtain approval of the product candidate (including a medical device) by the comparable regulatory authorities of countries outside the US before we can commence clinical studies or marketing of the product candidate 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 with EU standards, and therefore recognize the CE mark as a declaration of conformity to applicable standards. Furthermore, we must obtain any required pricing approvals in addition to regulatory approval prior to launching a product candidate 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 ongoing 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).

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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.

Early Access Programs in the European Union

Under EU 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 that must be approved through the centralized procedure, such as orphan drugs, compassionate use programs are also regulated at the European level. ARIKAYCE is available in certain European countries under early access programs.

Special programs can be set up to make available to patients with an unmet medical need a promising drug 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 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. Generally, doctors who wish to obtain a promising drug for 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 a system is in place to record any side effects reported by the patients or their doctors. Orphan drugs very 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 long time required for both their approval and effective marketing.

Doctors can also obtain certain drugs for their patients by requesting a supply of a drug from the manufacturer or a pharmacist located in another country, to be used for an individual patient under their direct responsibility. This is often called treatment on a 'named-patient basis' and is distinct from compassionate use programs. In this case, the doctor responsible for the treatment will either contact the manufacturer directly or issue a prescription to be fulfilled by a pharmacist. While manufacturers or pharmacists do record what they supply, there is no central register of the 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

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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.

As one of the conditions for obtaining Medicaid and Medicare Part B coverage for our marketed pharmaceutical products, 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 by federal statutes to receive drugs 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. We may also be subject to penalties for improper marketing, including off-label marketing, of our drugs that are reimbursed by Medicare and Medicaid.

Private healthcare payers also attempt to control costs and influence drug pricing through a variety of mechanisms, including through negotiating discounts with the manufacturers and through the use of tiered formularies and other mechanisms that provide preferential access to certain drugs over others within a therapeutic class. Payers also set other criteria to govern the uses of a drug that will be deemed medically appropriate and therefore reimbursed or otherwise covered. The newly elected US President has indicated an interest in having the federal government negotiate drug prices with pharmaceutical manufacturers.

Different pricing and reimbursement schemes exist in other countries. In the EU, governments influence the price of drugs 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 patients. Some jurisdictions operate positive and negative list systems under which drugs 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 drugs, 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 drugs. 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 drugs will allow favorable reimbursement and pricing arrangements for any of our products.

Fraud and Abuse and Other 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 US and most jurisdictions, numerous detailed requirements apply to government and private health care programs, and a broad range of fraud and abuse and transparency laws are relevant to pharmaceutical companies. US federal and state healthcare laws and regulations in these areas include the following:

- The federal anti-kickback statute;
- 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;

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- The federal criminal false statements statute;
- The price reporting requirements under the Medicaid Drug Rebate Program and the Veterans Health Care Act of 1992;
- The federal Physician Payment Sunshine Act, being implemented as the Open Payments Program; and
- Analogous and similar state laws and regulations.

Similar restrictions apply in the member states of the EU, which have been set out by laws or industry codes of conducts.

Employees

As of December 31, 2016, we had a total of 161 employees, including 86 in research, clinical, regulatory, medical affairs and quality assurance; 17 in technical operations, manufacturing and quality control; 42 in general and administrative functions; and 16 in pre-commercial activities. We had 140 employees in the US and 21 employees in Europe. We anticipate increasing our headcount in 2017.

None of our employees are represented by a labor union and we believe that our relations with our employees are generally good. Generally, 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 (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 (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, 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 1-800-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, and 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, financial condition, results of operations, the value of our common stock and our prospects 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 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 addition, even if we believe our clinical trials demonstrate promising results, regulators may decline to grant regulatory approval conditional or otherwise. Further, even if we subsequently obtain conditional approval, it may be withdrawn under certain circumstances and confirmatory clinical studies may be required and could fail to demonstrate sufficient safety and efficacy to obtain full approval.

We are conducting a global phase 3 clinical study of ARIKAYCE (the 212 or CONVERT study) in adult non-CF patients with NTM lung infections caused by MAC that are refractory to treatment. The CONVERT study is designed to confirm the culture conversion results seen in our phase 2 clinical trial (the 112 study). CONVERT study subjects who are non-converters by Month 6 may be eligible to enter a separate 12-month open-label study (the 312 study). The primary objective of the 312 study is to evaluate the long-term safety and tolerability of ARIKAYCE in combination with a standard multi-drug regimen. The clinical trial process may fail to demonstrate with statistical significance that our drug product candidates are effective for the proposed indications, or may fail to establish adequate safety. Such failure may cause us to abandon a drug product candidate and may delay development of other drug product candidates.

In the fourth quarter of 2014, we filed an MAA with the EMA for ARIKAYCE as a treatment for NTM lung disease in adult patients and for cystic fibrosis (CF) patients with *Pseudomonas* lung

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infections. The filing was based on data from our phase 3 study in CF patients with *Pseudomonas* and our phase 2 study in patients with NTM. In February 2015, the EMA validated our MAA as complete for review. The EMA subsequently requested additional information with respect to the CF indication regarding the similarity of ARIKAYCE to another product that has an orphan designation for the same *Pseudomonas* indication. In the third quarter of 2015, the EMA adopted our request to withdraw the *Pseudomonas* indication from our MAA. In April 2016, we submitted our written responses to the EMA's 180-day list of outstanding issues (LOI). In May 2016, we participated in an oral explanation meeting with the CHMP for the NTM indication to address the LOI. After the oral explanation meeting, the CHMP concluded that the data submitted did not provide enough evidence to support an approval. In June 2016, we withdrew our MAA. We intend to resubmit our MAA when sufficient clinical data are available.

We do not expect ARIKAYCE or any other drug candidates we may develop to be commercially available in any market until we receive requisite approval from the FDA, EMA or equivalent regulatory agency. The failure to obtain such approvals may materially adversely affect our business, financial condition, results of operations, the value of our common stock and our prospects.

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, and the failure to do so will prevent us from commercializing our products, which would materially adversely affect our business, financial condition, results of operations, prospects and the value of our common stock. The regulatory review and approval processes in both the US and Europe require evaluation of preclinical studies and clinical 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. For example, FDA has designated ARIKAYCE for fast track, breakthrough therapy and QIDP status, all programs intended to expedite or streamline the development and regulatory review of the drug. If we were to lose the current designation under one or more of those programs, we could face delays in the FDA review and approval process. 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. Even with these designations, there is no guarantee we will receive approval for ARIKAYCE on a timely basis, or at all. Similarly, we are defining our regulatory strategies to potentially secure US and EU orphan drug designations and expedite the development and regulatory review of INS1007 through programs such as US fast track designation and breakthrough therapy, but we may be unable to obtain them. In addition, although we believe that INS1009 could be eligible for approval under Section 505(b)(2) of the FDCA, and thus could rely at least in part on studies not

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conducted by or for us and for which we do not have a right of reference, we may not obtain approval from the FDA to use this pathway.

Approval by the FDA or the EMA does not ensure approval by the regulatory authorities of other countries. To market our products outside of the US and Europe we, and potentially our third party providers, 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. In addition, we may be subject to fines, suspension or withdrawal of marketing approvals, product recalls, seizure of products, operating restrictions (including with respect to our target market) and criminal prosecution if we fail to comply with applicable US and foreign regulatory requirements.

We have not completed the research and development stage of ARIKAYCE or any other product candidates. If we are unable to successfully commercialize ARIKAYCE or any other products, it may materially adversely affect our business, financial condition, results of operations, the value of our common stock and our prospects.

Our long-term viability and growth depend on the successful commercialization of ARIKAYCE and potentially other product candidates. 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 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 GLP and GCP and disease-specific expectations of the FDA and other regulatory bodies;
- Select and recruit clinical investigators and 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 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 associated with that product. 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, or regulators may require additional testing to substantiate our claims. If we do not proceed with the development of our ARIKAYCE program in the NTM lung disease 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, the value of our common stock, and our prospects.

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If 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, Japan 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.

Preclinical and clinical testing is expensive, difficult to design and implement and can take many years to complete. Special challenges can arise in conducting trials in diseases or conditions with small populations, such as difficulties enrolling adequate numbers of patients. 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 (IRBs) 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 experience diffculties or delays due to the number of clinical sites involved in our clinical trials;
- 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, IRBs 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 IRBs 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 IRBs 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;
- 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;
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- Shortening of the patent protection period during which we may have the exclusive right to commercialize our product candidates; and
- Our competitors may be able to bring products to market before we do.

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For example, results from our rat carcinogenicity study showed that when rats were given ARIKAYCE daily by inhalation for two years, two of the 120 rats receiving the highest dose developed lung carcinomas. 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 the results from this rat carcinogenicity study. In addition, we withdrew our MAA for ARIKAYCE in June 2016 after the CHMP concluded the data underlying it did not provide enough evidence to support approval, thereby delaying approval and commercialization of ARIKAYCE in Europe.

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.

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:

- Experience increased product development costs, as we have in the past;
- Be delayed in obtaining, or be unable 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;
- Have the product removed from the market after obtaining marketing approval; or
- Face a shortened patent protection period during which we may have the exclusive right to commercialize 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 the 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 adversely affect our business, financial condition, results of operations, the value of our common stock and our prospects.

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We may not be able to enroll enough patients to complete our clinical trials or retain a sufficient number of patients in our clinical trials to generate the data necessary for regulatory approval of our product candidates.

The completion rate of our clinical studies 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;
- Discontinue rates; and
- Competition from other companies' potential clinical studies for the same patient population

Delays in patient enrollment for future clinical trials, such as those we encountered in enrolling the CONVERT study, could increase costs and delay ultimate commercialization and sales, if any, of our products. We achieved our enrollment objective for the CONVERT study in the fourth quarter of 2016. The CONVERT study was designed to enroll enough subjects to ensure a sufficient number of patients are evaluable for the primary endpoint. Once enrolled, patients may elect to discontinue participation in a clinical trial at any time. If patients elect to discontinue participation in our clinical trials at a higher rate than expected, we may be unable to generate the data required by regulators for approval of our product candidates.

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 our product candidates to market, they may not gain market acceptance by physicians, patients, third-party payers and others in the medical community. If ARIKAYCE, or any other product candidate we bring to market, does 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 and reimbursement.

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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 to commercialize 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, our ability to generate product revenues will be adversely affected.

We have a small commercial organization for the marketing, market access, sales and distribution of our 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 will be expensive and time consuming and could delay any product launch, and we may be unable 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 in certain markets. 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 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.

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 currently have limited operations outside of the US. As of December 31, 2016, we had 21 employees located in Europe, and we have suppliers located around the world. In order to meet our long-term goals, we will need to grow our international operations over the next several years, including in Japan, and continue to source material used in the manufacture of our product candidates from abroad. Consequently, we are and will continue to be subject to additional risks related to operating in foreign countries, including:

- Our limited experience operating our business internationally;
- An inability to achieve the optimal pricing and reimbursement for ARIKAYCE or subsequent changes in reimbursement, pricing and other regulatory requirements;
- Any implementation of, or changes to, tariffs, trade barriers and other import-export regulations in the US or other countries in which we operate;
- Unexpected adverse events related to ARIKAYCE or our other product candidates occurring in foreign markets that we have not experienced in the US;
- Economic and political conditions, including geopolitical events, such as war and terrorism, foreign currency fluctuations and inflation, 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;

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- Changes resulting from (i) the uncertainty and instability in economic and market conditions caused by the UK's vote to exit the European Union; and (ii) the uncertainty regarding how the UK's access to the EU Single Market and the wider trading, legal, regulatory and labor environments, especially in the UK and European Union, will be impacted by the UK's vote to exit the European Union, including the resulting impact on our business; and
- Compliance with foreign or US 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 US laws.

These and other risks associated with our international operations may materially adversely affect our business, financial condition, results of operations and the value of our common stock.

If estimates of the size of the potential markets for our product candidates are overstated or regulators limit the proposed treatment population for our product candidates, our ability to commercialize such product candidates successfully or achieve sufficient revenue to support our business could be materially adversely affected.

We have relied on market research, funded by us and third parties, and certain government publications to estimate the potential market opportunity for NTM lung disease and we expect to do so in the future with respect to market opportunities for other product candidates. Development of such estimates, however, necessarily requires a number of assumptions subject to significant judgment, and such assumptions, as well as the resulting market opportunity estimates, could prove to be inaccurate. In addition, a potential market opportunity could be reduced if a regulator limits the proposed treatment population for a product candidate. In such circumstances, even if we obtain regulatory approval for a product candidate, we may be unable to commercialize it on a scale sufficient to generate material revenues, which could have a material adverse effect on our business, results of operations, financial condition, the value of our common stock and our prospects.

Risks Related to Our Reliance on Third Parties

We rely on third parties including collaborators, CROs, clinical and analytical laboratories, CMOs and other providers for many services that are critical to our business. If we are unable to form and sustain these relationships, or if any third-party arrangements that we may enter into are unsuccessful, including due to non-compliance by such third parties with our agreements or applicable law, 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, clinical development and manufacturing of our product candidates. For example, almost all of our clinical trial work is done by CROs, such as Synteract, our CRO for both the 212 and 312 studies, and clinical laboratories. Reliance on these third parties poses a number of risks, including the following:

- Significant competition in seeking appropriate partners;
- The complex and time-consuming nature of negotiation, documentation and implementation of agreements with third parties in the pharmaceutical industry;
- Our potential inability to establish and implement collaborations or other alternative arrangements that we might pursue on favorable terms;

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- Our potential inability to control whether third parties devote sufficient resources to our programs or products, including with respect to meeting contractual deadlines;
- Our potential inability to control the regulatory and contractual compliance of third parties, 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, including CROs, that result in a dispute over and loss of intellectual property rights, delay or termination of research, development, or commercialization of product candidates or litigation or arbitration;
- Contracts with our collaborators that fail to provide sufficient protection of our intellectual property; and
- Difficulty enforcing the contracts if one of these third parties fails to perform.

Such risks could materially harm our business, financial condition, results of operations, the value of our common stock and our prospects.

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, which would materially harm our business.

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. For instance, we are and expect to remain dependent upon Althea and Therapure being able to provide an adequate supply of ARIKAYCE both for our clinical trials and for commercial sale in the event ARIKAYCE receives marketing approvals. Althea currently manufactures ARIKAYCE at a relatively small scale. In order to meet potential commercial demand, if ARIKAYCE is approved, we have constructed a manufacturing operation at Therapure in Canada that operates at a larger scale. We may not be able to secure an alternative source of ARIKAYCE at an adequate scale of production should either of these suppliers be unable to provide us with ARIKAYCE.

We are also 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, as PARI is the sole manufacturer of the eFlow Nebulizer System. We have no alternative supplier for the Device, and we do not intend to seek an alternative or secondary supplier. Significant effort and time were expended in the optimization of the nebulizer for use with ARIKAYCE. In the event PARI cannot provide us with sufficient quantities of the Device, replication of the optimized device by another party may require considerable time and additional regulatory approval. In the case of certain defined supply failures, we will have the right under the Commercialization Agreement to make the Device and have it made by certain third parties, but not those deemed under the Commercialization Agreement to compete with PARI.

We do not have long-term commercial agreements with all of our suppliers 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. For instance, an inadequate supply of ARIKAYCE or the Device could delay, impair or prevent clinical trials, the development and commercialization of ARIKAYCE and adversely affect our business, financial condition, results of operations, the value of our common stock and our prospects.

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,

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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. The FDA evaluates the information contained in such disclosures to determine whether disclosed interests may have an impact on the reliability of a study. If the FDA determines that financial interests of any clinical investigator raise serious questions of data integrity, the 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 the FDA that a financial relationship of an investigator raises serious questions of data integrity, could delay or otherwise adversely affect approval of our products.

Risks Related to Our Financial Condition and Capital Requirements

We have a history of operating losses, and we currently have no material source of revenue. We expect to incur operating losses for the foreseeable future and may never achieve or maintain profitability.

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 and we did not generate material revenue in 2016, 2015 or 2014. 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 significantly expand our sales and marketing organization and establish 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, 2016, our accumulated deficit was $765.2 million. For the year ended December 31, 2016, our consolidated net loss was $176.3 million. To achieve and maintain profitability, we need to generate significant revenues from future product sales. The process of developing and commercializing our products will require significant expenditures for pre-clinical and clinical testing, regulatory approvals for commercialization and marketing, development of an internal or external sales and marketing organization and other related activities. Because of the numerous risks and uncertainties associated with drug development and commercialization, we are unable to predict the extent of any future losses, and we may never generate significant future revenues or achieve and sustain profitability.

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 will need to seek additional funding in order to complete any clinical trials related to ARIKAYCE, seek regulatory approvals of ARIKAYCE, and commercially launch ARIKAYCE, including due to changes in our product development plans or misjudgment of expected costs. We also may require additional future capital in order to continue our other research and development activities, fund corporate development, maintain our intellectual property portfolio or resolve litigation. As of December 31, 2016, we had $162.6 million of cash and cash equivalents on hand but no committed sources of capital. We do not know whether additional financing will be available when needed, or, if available, that the terms will be favorable. 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, which would likely have a material adverse effect on our business and prospects, as well as the value of our common stock.

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

Our A&R Loan Agreement 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 shareholders. The loan agreement also contains certain other covenants (including limitations on other indebtedness, liens, acquisitions, investments and dividends). 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 A&R Loan Agreement. In addition, pursuant to the A&R Loan Agreement, the lender has the right to participate, in an amount of up to $2.0 million, in a subsequent private financing that involves the issuance of our equity securities.

The interest-only period under the A&R Loan Agreement extends through November 1, 2018, and can only be extended up to six months under certain conditions. The maturity date of the loan facility is October 1, 2020. Pursuant to the A&R Loan Agreement, we are required to have a consolidated minimum cash liquidity in an amount no less than $25.0 million. Such requirement terminates upon the earlier of the date by which we complete an equity financing with at least $75.0 million in proceeds or the date we generate and announce data from the CONVERT study in a manner that could support an NDA filing.

Our borrowings under the A&R Loan Agreement are secured by a lien on our assets, excluding our intellectual property, and in the event of a default on the loan, Hercules may have the right to seize our assets securing our obligations under the A&R Loan Agreement. The terms and restrictions provided for in the A&R Loan Agreement may inhibit our ability to conduct our business and to maximize shareholder value. 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 24% of our total assets. A reduction in the value of our IPRD could have a material adverse effect on our results of operations, financial condition and the value of our common stock.

As a result of the merger with Transave in 2010, we recorded an intangible IPRD asset of $77.9 million and goodwill of $6.3 million on our balance sheet. As a result of the clinical hold on ARIKAYCE announced in late 2011, we recorded a charge of $26.0 million in the fourth quarter of 2011 that 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 could materially adversely affect our results of operations, financial condition and the value of our common stock.

We may be unable to use our net operating losses.

We have substantial tax loss carry forwards for US federal income tax and state income tax purposes and beginning in 2015, we have tax loss carry forwards in Ireland as well. Our ability to fully use certain US tax loss carry forwards prior to December 2010 to offset future income or tax liability is 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 options, may limit or eliminate our ability to use certain net operating losses in the future.

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Any acquisitions we make, or collaborative relationships we enter into, may require a significant amount of our available cash and may not be scientifically or commercially successful.

As part of our business strategy, we may effect acquisitions to obtain additional businesses, products, technologies, capabilities and personnel, but we cannot assure you that we will identify suitable products or enter into such acquisitions on acceptable terms.

Acquisitions involve a number of operational risks, including:

- Failure to achieve expected synergies;
- Difficulty and expense of assimilating the operations, technology and personnel of the acquired business;
- Our inability to retain the management, key personnel and other employees of the acquired business;
- Our inability to maintain the acquired company's relationship with key third parties, such as alliance partners;
- Exposure to legal claims for activities of the acquired business prior to the acquisition;
- The diversion of our management's attention from our core business; and
- The potential impairment of goodwill and write-off of in-process research and development costs, adversely affecting our reported results of operations and financial condition.

We also 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.

If we make one or more significant acquisitions or enter into a significant collaboration in which the consideration includes cash, we may be required to use a substantial portion of our available cash and/or need to raise additional capital. For instance, in September and October of 2016, we borrowed $30.0 million under the A&R Loan Agreement to fund the payment due under the AZ License Agreement, and this investment as with any acquisition or collaboration may not be successful.

Risks Related to Regulatory Matters

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, which could delay commercialization of our product candidates or subject us to the risk of having any approval withdrawn.

The 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). We are using a surrogate endpoint in our CONVERT study. Developing clinical endpoints that are unsatisfactory to regulators could delay clinical trials and the FDA approval process which could materially adversely affect our business, financial condition, results of operations, the value of our common stock and our prospects.

If one or more of our product candidates is approved based on a surrogate or an intermediate clinical endpoint under the accelerated approval regulations, the approval will be subject to the requirement that we study the product candidate further to verify and describe its clinical benefit,

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where there is uncertainty as to the relation of the surrogate or intermediate clinical endpoint to clinical benefit or of the observed clinical benefit to the ultimate outcome. Thus, even if we are successful in obtaining accelerated approval in the US or under comparable pathways in other jurisdictions, we may face requirements and limitations that will adversely affect our prospects. For example, we may not successfully complete required post-approval trials, or such trials may not confirm the clinical benefit of our drug, and we may be required to withdraw approval of the drug.

For ARIKAYCE to be successfully developed and commercialized in a given market, 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 by regulators.

The eFlow Nebulizer System must receive regulatory approval in order for us to develop and commercialize ARIKAYCE. Although the optimized eFlow Nebulizer System is CE marked by PARI the EU, outside the EU, it is labeled as investigational for use in our clinical trials in the US, Japan, Canada and Australia. 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. We continue to work closely with PARI to coordinate efforts regarding regulatory requirements, including our proposed filings for a drug and device. However, we or PARI may not be successful in meeting the regulatory requirements for the eFlow Nebulizer System, which would prevent or hinder our ability to bring ARIKAYCE to market or market it successfully.

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 (REMS), 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;
- Compliance with cGMPs;
- 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 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 (PDMA);
- Sales, marketing and scientific or educational grant programs must comply with federal and state laws; and
- Pricing and rebate programs must comply with the Medicaid rebate requirements, and if products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply.

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

If we 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; and/or
- 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.

The manufacturing facilities of our third party manufacturers are subject to significant government regulations and approvals, which are often costly and could result in adverse consequences to our business if we and our manufacturing partner fail to comply with the regulations or maintain the approvals.

Manufacturers of our product candidates are subject to cGMP and similar standards, and we do not have control over compliance with these regulations by our manufacturers. If one of them fails to obtain or maintain compliance or experiences problems in the scale-up of commercial production, the production of our product candidates could be interrupted, resulting in delays, additional costs or restrictions on the marketing or sale of our products. In addition, these manufacturers and their facilities will be subject to continual review and periodic inspections by the FDA and other regulatory authorities following regulatory approval, if any, of our product candidates. For instance, to monitor compliance with applicable regulations, the FDA routinely conducts inspections of facilities and may identify potential deficiencies. For example, the FDA issues what are referred to as "FDA Form 483s" that set forth observations and concerns that are identified during its inspections. Failure to satisfactorily address the concerns or potential deficiencies identified in a Form 483 could result in the issuance of a warning letter, which is a notice of the issues that the FDA believes to be significant regulatory violations requiring prompt corrective actions. Failure to respond adequately to a warning letter, or to otherwise fail to comply with applicable regulatory requirements could result in enforcement, remedial and/or punitive actions by the FDA or other regulatory authorities.

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

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they were used in clinical trials. This discovery could have a number of potentially significant negative consequences, including:

- Regulatory authorities may withdraw their approval of the product and may require recall of product in distribution;
- Regulatory authorities may require the addition of labeling statements, such as black box or other warnings or contraindications, or the issuance of "Dear Doctor Letters" or similar communications to healthcare professionals;
- Regulatory authorities may impose additional restrictions on marketing and distribution of the products, or other risk management measures, such as a REMS;
- 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; and
- We could be subject to negative publicity, including communications issued by regulatory authorities.

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

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 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.

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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. For instance, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) expanded Medicare outpatient prescription drug coverage for the elderly through Part D prescription drug plans sponsored by private entities and authorized such plans to use formularies where they can limit the number of drugs that will be covered in any therapeutic class. The plans generally negotiate significant price concessions as a condition of formulary placement. The MMA also introduced a new reimbursement methodology based on average sales prices for physician-administered drugs, which is generally believed to have resulted in lower Medicare reimbursement for physician-administered drugs. These cost reduction initiatives and other provisions of this legislation provide additional pressure to contain and reduce drug prices and 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. Additionally, the Patient Protection and Affordable Care Act (ACA) revised the definition of "average manufacturer price" for reporting purposes, which could increase the amount of Medicaid drug rebates to states, and has imposed a significant annual fee on companies that manufacture or import branded prescription drug products. We believe it is likely that the ACA, or any legislation enacted to replace it, 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 and/or the newly elected US President, 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 ACA 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.

Government health care reform could increase our costs, and could materially adversely affect our business, financial condition, results of operations, the value of our common stock and our prospects.

Our industry is highly regulated and changes in or revisions to laws and regulations that make gaining regulatory approval, reimbursement and pricing more difficult or subject to different criteria and standards may adversely impact our business, operations or financial results. For example, under the ACA, drug manufacturers are required to report information on payments or transfers of value to US physicians and teaching hospitals as well as investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties. The reported data is posted in searchable form on a public website. In addition, some states, as well as other countries, including France, require the disclosure of certain payments to health care

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professionals. In the coming years, we expect additional and potentially substantial, changes to governmental programs that could significantly impact the success of our product candidates.

The new Administration and the majority party in both Houses of Congress have indicated their desire to repeal the ACA. It is unclear whether, when and how that repeal will be effectuated and what the effect on the healthcare sector will be. The new US President has indicated an interest in having the federal government negotiate drug prices with pharmaceutical manufacturers. Changes to the ACA, to the Medicare or Medicaid programs, or to the ability of the federal government to negotiate drug prices, or other federal legislation regarding healthcare access, financing or legislation in individual states, could affect our business, financial condition, results of operations, the value of our common stock and our prospects.

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. 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.

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 US, 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. 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 these laws. 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 US government, and our business, financial condition, and results of operations and the value of our common stock may be adversely affected. Our reputation could also suffer. In addition, private individuals have the ability to bring actions on behalf of the government under the federal FCA as well as under the false claims laws of several states.

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

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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.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal, technical, scientific and factual questions, and our success depends in large part on our ability to protect our proprietary technology and to obtain patent protection for our products, prevent third parties from infringing on our patents, both domestically and internationally. We have sought to protect our proprietary position by filing patent applications in the US and abroad related to our novel technologies and products that are important to our business. This process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technologies or from developing competing products and technologies.

Even if our owned and licensed patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Any conclusions we may reach regarding non-infringement, inapplicability or invalidity of a third party's intellectual property vis-à-vis our proprietary rights, or those of a licensor, 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 render these conclusions inaccurate. Our competitors may also be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

Additionally, patents issued to us or our licensors may be challenged, narrowed, invalidated, held to be unenforceable or circumvented through litigation, 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. US patents and patent applications may also be subject to interference or derivation proceedings, and US patents may be subject to re-examination proceedings, reissue, post-grant review and/or inter partes review in the USPTO. Foreign patents may be subject to opposition or comparable proceedings in the corresponding foreign patent office, which could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. See *Intellectual Property ARIKAYCE Patents and Trade Secrets* for information on our European Patent that is being opposed by Generics (UK) Ltd.

Changes in either patent laws or in interpretations of patent laws in the US and other countries may also diminish the value of our intellectual property or narrow the scope of our patent protection, including making it easier for competitors to challenge our patents. For example, the America Invents Act included a number of changes to established practices, including the transition to a first-inventor-to-file system and new procedures for challenging patents and implementation of different methods for invalidating patents.

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 continues to consider 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 whether and how the FDA's disclosure policies may change in the future.

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 US. 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 patents or 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 may be required to 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. 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 US and foreign countries may affect our ability to obtain adequate protection for our technology and to enforce intellectual property rights.

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. Any existing third-party patents, or patents that may later issue to third parties, could negatively affect our commercialization of ARIKAYCE, INS1007, INS1009 or any other product. For instance, 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; however, a competitor in the PAH indication may claim that we or our supplier have infringed upon or misappropriated its proprietary rights. 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 take actions including but not limited to the following:

- 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; and/or

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- Obtain one or more licenses arising out of a settlement of litigation or otherwise from third parties which license(s) may not be available to us on acceptable terms or at all.

Such litigation, and any resulting resolution, could have a material adverse effect on our business, financial condition, results of operations, the value of our common stock and our prospects.

Any lawsuits or other proceedings relating to infringement by us or third parties of intellectual property rights may be costly and time consuming.

We may have to undertake costly litigation or engage in other proceedings, such as interference or inter partes review, to enforce any patents issued or licensed to us, to confirm the scope and validity of our or a licensor's proprietary rights or to defend against allegations that we have infringed a third party's intellectual property rights. Such proceedings are also likely to be time consuming and may divert management attention from operation of our business.

If we fail to comply with our obligations in the agreements under which we license rights to technology from third parties, or if the license agreements are terminated for other reasons, we could lose license rights that are important to our business.

We are a party to licensing agreements with PARI and AZ, which we view as material to our business. For additional information regarding the terms of these agreements, see *Business License and Other Agreements*. If we fail to comply with our obligations under these agreements, our counterparty may have the right to take action against us, up to and including termination of the relevant license. For instance, under our licensing agreement with PARI, with respect to NTM, CF and bronchiectasis, we have specific obligations to use commercially reasonable efforts to achieve certain developmental and regulatory milestones by set deadlines. Additionally, for NTM, we are obligated to use commercially reasonable efforts to achieve certain commercial milestones in the US, Europe and Canada. The consequences of our failing to use commercially reasonable efforts to achieve certain commercial milestones are context-specific, but include ending PARI's non-compete obligation, making the license non-exclusive and terminating the license, in each case with respect to the applicable indication. Similarly, under the AZ License Agreement, AstraZeneca may terminate our license to INS1007 if we fail to use commercially reasonable efforts to develop and commercialize a product based on INS1007, or we are subject to a bankruptcy or insolvency. Reduction or elimination of our licensed rights may result in our having to negotiate new or reinstated licenses with less favorable terms and may materially harm our business.

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. 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

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manufacturing 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. Our competitors may also use different technologies or approaches to the development of products similar to the products we are seeking to develop.

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. For instance, 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 or our other product candidates, it would likely materially 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 or other countries where we may sell ARIKAYCE.

In the event there are other amikacin products approved by the FDA or other regulatory agencies 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 regulations prohibit a drug company from promoting off-label use of its product, the FDA and other regulatory agencies do not regulate the practice of medicine and 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 or other regulatory agency approval, even if such use violates our patents or orphan drug exclusivity for the use of amikacin to treat such diseases. If we are unable to compete successfully, it will materially adversely affect our business, financial condition, results of operations, the value of our common stock and our prospects.

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. 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* for additional information. 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.

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 US for the first product in a class licensed for the treatment of a rare disease. Orphan exclusivity does not, however, bar approval of

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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. The 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, the 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 and could have a material adverse effect on our business.

Our research, development and manufacturing activities used in the production of ARIKAYCE involve the use of hazardous materials, which could expose us to damages, fines, penalties and sanctions 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 and our other product candidates 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 strive to comply 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 CMOs or other third parties. Any such liability, or even allegations 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, which can lead to significant adverse publicity and obligations to pay damages. 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.

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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 materially harm our business, financial condition, results of operations, the value of our common stock and our prospects.

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 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, including those discussed herein, many of which are beyond our control. 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

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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. As described below, a securities class action lawsuit was initiated against us during 2016 following a decline in our stock price.

We and certain of our officers and directors are subject to a securities class action lawsuit, which may require significant management and board time and attention and significant legal expenses and may result in an unfavorable outcome, which could have a material adverse effect on our business, financial condition, results of operations and cash flows.

We and certain of our executive officers and directors have been named as defendants in a securities class action lawsuit initially filed on July 15, 2016. The amended complaint, filed December 15, 2016, alleges that we and certain of our executive officers and directors violated Sections 11 and 12(a)(2) of the Securities Act of 1933, as amended (Securities Act), and that we and certain of our executive officers violated Section 10(b) of the Exchange Act, Rule 10b-5 promulgated thereunder of the Exchange Act, by making materially false or misleading statements and omissions relating to the development of ARIKAYCE and/or related requests for regulatory approval. It also alleges that the defendant officers and directors violated Section 15 of the Securities Act and that the defendant officers violated Section 20(a) of the Exchange Act. For additional information, see Item 3, *Legal Proceedings*. While we believe that we have substantial legal and factual defenses to the claims in the class action and intend to vigorously defend the case, this lawsuit could divert our management's and board's attention from other business matters, the outcome of the pending litigation is difficult to predict and quantify, and the defense against the underlying claims will likely be costly. The ultimate resolution of this matter could result in payments of monetary damages or other costs, materially and adversely affect our business, financial condition, results of operations and cash flows, or adversely affect our reputation, and consequently, could negatively impact the price of our common stock.

We have insurance policies related to the risks associated with our business, including directors' and officers' liability insurance policies. However, there is no assurance that our insurance coverage will be sufficient or that our insurance carriers will cover all claims in that litigation. If we are not successful in our defense of the claims asserted in the putative action and those claims are not covered by insurance or exceed our insurance coverage, we may have to pay damage awards, indemnify our officers from damage awards that may be entered against them and pay the costs and expenses incurred in defense of, or in any settlement of, such claims.

In addition, there is the potential for additional shareholder litigation against us, and we could be materially and adversely affected by such matters.

Future issuances of our common stock will dilute the ownership interest of our existing shareholders and such issuances, or the possibility of such issuances, could adversely affect prevailing market prices for our common stock or our future ability to raise capital through an offering of equity securities.

Our Articles of Incorporation currently authorize us to issue up to 500 million common shares. As of December 31, 2016, we had 62.0 million 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, such funding may significantly dilute existing shareholders. In addition, as of December 31, 2016, 7.2 million 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 similarly dilute the ownership interests of existing shareholders. In addition, sales in the public market of newly issued, or

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even the possibility of such sales, could adversely affect prevailing market prices of our common stock or our future ability to raise capital through an equity offering.

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:

- The ability 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;
- The 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 prohibition against 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 increase our costs of compliance, and our inability to satisfy these requirements could materially harm our business.

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 have high costs of compliance, and our failure to comply with such laws, regulations and standards may be detrimental to our business. 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. 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

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of our financial statements, which could cause the market price of our stock to decline, and substantial costs and resources to rectify any internal control deficiencies. 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. 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.

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, 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 materially harm our business.

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 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, our insurance may not cover all claims, continue to be available on reasonable terms or be sufficient in amount to cover one or more large claims; additionally, the insurer may 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.

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We are subject to the US Foreign Corrupt Practices Act, the UK Bribery Act and other anti-corruption laws and trade control laws, as well as other laws governing our operations. If we fail to comply with these laws, we could be subject to negative publicity, civil or criminal penalties, other remedial measures, and legal expenses, which could adversely affect our business, financial condition, results of operations and the price of our common stock.

Our operations are subject to anti-corruption laws, including the US Foreign Corrupt Practices Act (FCPA), the UK Bribery Act and other anti-corruption laws that apply in countries where we do business. The FCPA, UK Bribery Act and these other laws generally prohibit us, our employees and our intermediaries from making prohibited payments to government officials or other persons to obtain or retain business or gain some other business advantage. We are conducting the CONVERT study at more than 125 sites in 18 countries around the world, and certain of these jurisdictions in which we operate pose a risk of potential FCPA violations, and we participate in joint ventures and relationships with third parties whose actions could potentially subject us to liability under the FCPA or local anti-corruption laws. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the U.S. Department of Commerce's Bureau of Industry and Security, the U.S. Department of Treasury's Office of Foreign Asset Control, and various non-US government entities, including applicable export control regulations, economic sanctions on countries and persons, customs requirements, currency exchange regulations and transfer pricing regulations (collectively, Trade Control laws).

We may not be effective in ensuring our compliance with all applicable anticorruption laws, including the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations, and the price of our common stock. Likewise, even an investigation by US or foreign authorities of potential violations of the FCPA other anti-corruption laws or Trade Control laws could have an adverse impact on our reputation, business, financial condition, results of operations and the price of our common stock.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

We currently lease 56,617 square feet of laboratory and office space in Bridgewater, New Jersey. The initial term of the lease will expire in November 2019, and we have the option to extend the lease for two additional five year periods beyond the initial term. In July 2016, we signed an operating lease for 13,274 square feet of additional laboratory space located in Bridgewater, NJ for which the initial lease term expires in September 2021. We also lease office space in Ireland and the Netherlands.

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ITEM 3. LEGAL PROCEEDINGS

On July 15, 2016, a lawsuit captioned Hoey v. Insmed Incorporated, et al, No. 3:16-cv-04323-FLW-TJB (D.N.J. July 15, 2016) was filed in the US District Court for the District of New Jersey on behalf of a putative class of investors who purchased our common stock from March 18, 2013 through June 8, 2016. The complaint alleged that the Company and certain of its executives violated Sections 10(b) and 20(a) of the Exchange Act by misrepresenting and/or omitting the likelihood of the EMA approving our European MAA for use of ARIKAYCE in the treatment of NTM lung disease and the likelihood of commercialization of ARIKAYCE in Europe.

On October 25, 2016, the Court issued an order appointing Bucks County Employees Retirement Fund as lead plaintiff for the putative class. On December 15, 2016, lead plaintiff filed an amended complaint that shortens the putative class period for the Exchange Act claims to March 26, 2014 through June 8, 2016 and adds claims under Sections 11, 12, and 15 of the Securities Act on behalf of a putative class of investors who purchased common stock in or traceable to our March 31, 2015 public offering. The amended complaint names as defendants in the Securities Act claims the Company, certain directors and officers, and the investment banks who served as underwriters in connection with the secondary offering. The amended complaint alleges defendants violated the Securities Act by using a purportedly misleading definition of "culture conversion" and supposedly failing to disclose in the offering materials purported flaws in the Phase 2 study that made the secondary offering risky or speculative. The amended complaint seeks damages in an unspecified amount. Our response to the amended complaint, which we intend to move to dismiss, is due by March 1, 2017. We believe that the allegations in the complaints are without merit and intend to defend the lawsuit vigorously; however, there can be no assurance regarding the ultimate outcome of the lawsuit.

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.

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 2016 and 2015.

Fiscal Year 2016	**High**	**Low**
Fourth Quarter	$ 15.49	$ 10.21
Third Quarter	$ 15.35	$ 9.75
Second Quarter	$ 14.53	$ 9.02
First Quarter	$ 18.60	$ 10.53

Fiscal Year 2015	**High**	**Low**
Fourth Quarter	$ 21.14	$ 15.31
Third Quarter	$ 28.66	$ 17.07
Second Quarter	$ 25.39	$ 19.87
First Quarter	$ 22.59	$ 13.93

On February 1, 2017, the last reported sale price for our common stock on the Nasdaq Global Select Market was $15.11 per share. As of February 1, 2017, there were 138 holders of record of our common stock.

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. Under the terms of our loan agreement with Hercules, we are prohibited from declaring or paying any cash dividend or making a cash distribution on any class of our stock or on other equity interest, except that our subsidiaries (defined in the loan agreement as a corporate entity in which we control more than 50% of the voting securities) may pay dividends or make distributions to their equity owners. Any future determination as to the payment of dividends will be dependent upon these and any contractual or other restrictions to which we may be subject and, to the extent permissible thereunder, 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 at that time.

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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 12/31/11 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, 2016, 2015, 2014, 2013 and 2012. 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,				
	2016	2015	2014	2013	2012
	(in thousands, except per share data)				
Historical Statement of Operations Data:					
Revenues	$ -	$ -	$ -	$ 11,500	$ -
Operating expenses:					
Research and development	122,721	74,277	56,292	44,279	29,781
General and administrative	50,679	43,216	31,073	22,236	12,657
Total operating expenses	173,400	117,493	87,365	66,515	42,438
Operating loss	(173,400)	(117,493)	(87,365)	(55,015)	(42,438)
Investment income	604	261	58	166	1,822
Interest expense	(3,498)	(2,889)	(2,415)	(2,412)	(763)
Other income (expense), net	119	(33)	141	(33)	5
Loss before income taxes	(176,175)	(120,154)	(89,581)	(57,294)	(41,374)
Income tax provision (benefit)	98	(1,971)	(10,422)	(1,221)	-
Net loss	$ (176,273)	$ (118,183)	$ (79,159)	$ (56,073)	$ (41,374)
Basic and diluted net loss per share	$ (2.85)	$ (2.02)	$ (1.84)	$ (1.60)	$ (1.56)
Weighted average basic and diluted common shares outstanding	61,892	58,633	43,095	34,980	26,545
Historical Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 162,591	$ 282,876	$ 159,226	$ 113,894	$ 90,782
Certificate of deposit	$ -	$ -	$ -	$ -	$ 2,153
Total assets	$ 237,956	$ 356,556	$ 230,864	$ 176,498	$ 153,561
Current portion of long-term debt	$ -	$ 3,113	$ -	$ 3,283	$ 3,007
Debt, long-term	$ 54,791	$ 22,027	$ 24,856	$ 16,338	$ 16,221
Total shareholders' equity	$ 154,483	$ 311,698	$ 186,237	$ 143,324	$ 120,882

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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 contained elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements that involve risks and uncertainties. As a result of many factors, such as those set forth under the section entitled Risk Factors, Cautionary Note Regarding Forward-Looking Statements and elsewhere herein, our actual results may differ materially from those anticipated in these forward-looking statements.

EXECUTIVE OVERVIEW

Insmed is a global biopharmaceutical company focused on the unmet needs of patients with rare diseases. 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 diseases. Our continuing operations are based on the technology and products historically developed by Transave. During 2015 we formed subsidiaries in a number of countries in Europe in preparation for the commercialization of ARIKAYCE, upon approval in the European Union, and to support our global tax structure. The Company has legal entities in the US, Ireland, Germany, France, the United Kingdom (UK) and the Netherlands.

We have not generated material revenue to date, except for in 2013, and through December 31, 2016, we had an accumulated deficit of $765.2 million. We have financed our operations primarily through the public offerings of our equity securities and debt financings. Although it is difficult to predict our future funding requirements, based upon our current operating plan, we anticipate that our cash and cash equivalents as of December 31, 2016 will enable us to fund our operations for at least the next 12 months.

We expect that over the next several years we will continue to incur losses from operations as we increase our expenditures in research and development in connection with our ongoing clinical trials, and for expenses related to the preparation for the commercial launch of ARIKAYCE globally, if approved. If adequate funds are not available to us on a timely basis, or at all, we may be required to terminate or delay certain development activities, or delay our investment in sales and marketing capabilities or other activities that may be necessary to commercialize ARIKAYCE, if we obtain marketing approval.

PIPELINE PROGRESS

ARIKAYCE

Our lead product candidate is ARIKAYCE, or liposomal amikacin for inhalation (LAI), which is in late-stage development for adult patients with treatment refractory nontuberculous mycobacteria (NTM) lung disease caused by *Mycobacterium avium* complex (MAC), a rare and often chronic infection that is capable of causing irreversible lung damage and which can be fatal.

In the fourth quarter of 2016, we completed enrollment in our global phase 3 clinical study of ARIKAYCE (the 212 or CONVERT study) in adult patients with treatment refractory NTM lung disease caused by MAC, which is the predominant infective species in NTM lung disease in the United States (US), Europe, and Japan. We expect to report top-line results for the Month 6 primary endpoint

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in the second half of 2017. If the CONVERT study meets its primary endpoint, we intend to seek accelerated marketing approval for ARIKAYCE in the US.

CONVERT study subjects who are non-converters by Month 6 may be eligible to enter a separate 12-month open-label study (the 312 study). The primary objective of the 312 study is to evaluate the long-term safety and tolerability of ARIKAYCE in combination with a standard multi-drug regimen.

In the fourth quarter of 2014, we filed an MAA with the European Medicines Agency (EMA) for ARIKAYCE as a treatment for NTM lung disease in adult patients and for cystic fibrosis (CF) patients with *Pseudomonas* lung infections. The filing was based on data from our phase 3 study in CF patients with *Pseudomonas* and our phase 2 study in patients with NTM. In February 2015, the EMA validated our MAA as complete for review. The EMA subsequently requested additional information with respect to the CF indication regarding the similarity of ARIKAYCE to another product that has an orphan designation for the same *Pseudomonas* indication. In the third quarter of 2015, the EMA adopted our request to withdraw the *Pseudomonas* indication from our MAA. In April 2016, we submitted our written responses to the EMA's 180-day list of outstanding issues (LOI). In May 2016, we participated in an oral explanation meeting with the CHMP for the NTM indication to address the LOI. After the oral explanation meeting, the CHMP concluded that the data submitted did not provide enough evidence to support an approval. In June 2016, we withdrew our MAA. We intend to seek marketing approval for ARIKAYCE in the EU, Japan and certain other countries outside the US when sufficient data are available.

INS1007

INS1007 is a novel oral reversible inhibitor of dipeptidyl peptidase 1 (DPP1), an enzyme responsible for activating neutrophil serine proteases, which are implicated in the pathology of chronic inflammatory lung diseases, such as non-cystic fibrosis (non-CF) bronchiectasis. In October 2016, we acquired the exclusive global rights to INS1007 (formerly known as AZD7986) from AstraZeneca and we are finalizing our plans for a phase 2 study in our lead indication, non-CF bronchiectasis. In a phase 1 study of healthy volunteers, AZD7986 was well tolerated and demonstrated inhibition of the activity of the neutrophil serine protease neutrophil elastase in a dose and concentration dependent manner. In preclinical studies, INS1007 was shown to reversibly inhibit DPP1 and the activation of neutrophil serine proteases within maturing neutrophils.

We are defining our regulatory strategies to potentially secure US and EU orphan drug designations and expedite the development and regulatory review of INS1007 through programs such as US fast track designation and breakthrough therapy. We plan to submit an Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) for non-CF bronchiectasis and subsequently commence a phase 2 clinical study of INS1007. The study is expected to begin in 2017. In addition, we are evaluating INS1007 in other potential indications.

INS1009

INS1009 is our inhaled nanoparticle formulation of a treprostinil prodrug that may offer a differentiated product profile for rare pulmonary disorders, including pulmonary arterial hypertension (PAH). We have completed a phase 1 study of INS1009 in healthy subjects and the results were presented at the European Respiratory Society international congress in September 2016. This first-in-human study of INS1009 determined the maximum-tolerated dose of a single dose of INS1009 and characterized a pharmacokinetic profile that supports once- or twice-daily dosing. The longer

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half-life of treprostinil associated with INS1009 was likely due to a sustained pulmonary release. We are currently evaluating our options to advance its development.

Other Development Activities

Our earlier-stage pipeline includes preclinical compounds that we are evaluating in multiple rare diseases of unmet medical need, including methicillin-resistant staph aureus (MRSA) and NTM. To complement our internal research and development, we actively evaluate in-licensing and acquisition opportunities for a broad range of rare diseases.

KEY COMPONENTS OF OUR RESULTS OF OPERATIONS

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. Expenses also include 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. In addition, our research and development expenses include payments to third parties for the license rights to products in development (prior to marketing approval), such as for INS1007. Our expenses related to manufacturing our drug candidate for clinical study are primarily related to activities at contract manufacturing organizations (CMOs) 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.

Since 2011, we have focused our development activities principally on our proprietary, advanced liposomal technology designed specifically for inhalation lung delivery. In 2015, we commenced the CONVERT study for ARIKAYCE for adult patients with treatment refractory NTM lung disease. In 2015, we also completed an open-label extension study in which CF patients that completed our phase 3 trial received ARIKAYCE for a period of two years. The majority of our research and development expenses have been for our ARIKAYCE development programs. Our development efforts in 2016 principally related to the development of ARIKAYCE in the NTM lung disease indication described above.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for our non-management directors and 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.

Investment Income and Interest Expense

Investment income consists of interest and dividend income earned on our cash and cash equivalents. Interest expense consists primarily of interest costs and amortization of debt issuance costs related to our debt obligations.

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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 other third party costs. Unamortized debt issuance costs associated with extinguished debt are expensed in the period of the extinguishment.

RESULTS OF OPERATIONS

Comparison of the Years Ended December 31, 2016 and 2015

Net Loss

Net loss for the year ended December 31, 2016 was $176.3 million, or $2.85 per common share basic and diluted, compared with a net loss of $118.2 million, or $2.02 per common share basic and diluted, for the year ended December 31, 2015. The $58.1 million increase in our net loss for the year ended December 31, 2016 as compared to the same period in 2015 was due to:

- Increased research and development expenses of $48.4 million primarily resulting from a $30.0 million upfront payment for the license agreement entered into with AstraZeneca AB (AstraZeneca) for exclusive global rights to INS1007 in October 2016 (AZ License Agreement), an increase in clinical trial expenses related to the CONVERT study and higher compensation and related expenses due to an increase in headcount; and
- Increased general and administrative expenses of $7.5 million resulting from an increase in pre-commercial planning activities, legal and consulting expenses and higher compensation and related expenses, including an increase in noncash stock-based compensation, related to an increase in headcount.

In addition, there was a $2.1 million decrease in the income tax benefit resulting from the sale of a portion of our New Jersey State net operating losses (NOLs) under the State of New Jersey's Technology Business Tax Certificate Transfer Program (the Program) for cash of $2.0 million in 2015.

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Research and Development Expenses

Research and development expenses for the years ended December 31, 2016 and 2015 were comprised of the following:

	Years Ended December 31,		Increase (decrease)	
	2016	2015	$	%
External Expenses				
Clinical development & research	$ 35,620	$ 25,274	$ 10,346	40.9%
INS1007 license payment	30,000	-	30,000	nm
Manufacturing	17,298	21,279	(3,981)	(18.7)%
Regulatory and quality assurance	2,510	3,051	(541)	(17.7)%
Subtotal external expenses	$ 85,428	$ 49,604	$ 35,824	72.2%
Internal Expenses				
Compensation and related expenses	$ 28,514	$ 18,666	$ 9,848	52.8%
Other internal operating expenses	8,779	6,007	2,772	46.1%
Subtotal internal expenses	$ 37,293	$ 24,673	$ 12,620	51.1%
Total	$ 122,721	$ 74,277	$ 48,444	65.2%

Research and development expenses increased to $122.7 million during the year ended December 31, 2016 from $74.3 million in the same period in 2015. The $48.4 million increase was due to a $30.0 million upfront payment under the AZ License Agreement related to INS1007 in October 2016, a $10.3 million increase in external clinical development expenses primarily related to the CONVERT study and a $9.8 million increase in compensation and related expenses, including stock-based compensation, due to an increase in headcount. These increases were partially offset by a $4.0 million decrease in manufacturing expenses primarily due to the completion of the build-out of our production area at Therapure's facility in 2015.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2016 and 2015 were comprised of the following:

	Year Ended December 31,		Increase (decrease)	
	2016	2015	$	%
General & administrative	$ 35,291	$ 30,614	$ 4,677	15.3%
Pre-commercial expenses	15,388	12,602	2,786	22.1%
Total general & administrative expenses	$ 50,679	$ 43,216	$ 7,463	17.3%

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General and administrative expenses increased to $50.7 million during the year ended December 31, 2016 from $43.2 million in the same period in 2015. The $7.5 million increase was primarily due to an increase of $3.7 million in consulting fees relating to pre-commercial planning activities, legal and consulting expenses and an increase of $3.7 million due to higher compensation costs, including stock-based compensation, related to an increase in headcount.

Interest Expense

Interest expense was $3.5 million during the year ended December 31, 2016 as compared to $2.9 million in the same period in 2015. The $0.6 million increase in interest expense in 2016 relates primarily to an increase in our borrowings from Hercules in September and October of 2016. We entered into an Amended and Restated Loan Agreement (A&R Loan Agreement) with Hercules which increased our borrowing capacity by an additional $30.0 million to an aggregate total of $55.0 million. The increase in borrowings under the A&R Loan Agreement was used to fund the upfront payment owed under the AZ License Agreement for the exclusive global rights to INS1007.

Income tax provision (benefit)

The income tax provision (benefit) was $0.1 million and $(2.0) million for the years ended December 31, 2016 and 2015, respectively. The income tax provision for the year ended December 31, 2016 reflects current income tax expense recorded as a result of taxable income in certain our subsidiaries in Europe. The income tax benefit recorded for the year ended December 31, 2015 primarily reflects the reversal of a valuation allowance previously recorded against our New Jersey State NOLs that resulted from the sale of a portion of our New Jersey State NOLs under the Program for cash of $2.0 million, 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. In 2015, we reached the lifetime maximum cap of NOLs that can be sold to the State of New Jersey. Therefore, we received no cash proceeds from the Program in 2016 and will not receive cash proceeds from the Program in the future.

Comparison of the Years Ended December 31, 2015 and 2014

Net Loss

Net loss for the year ended December 31, 2015 was $118.2 million, or ($2.02) per common share basic and diluted, compared with a net loss of $79.2 million, or ($1.84) per common share basic and diluted, for the year ended December 31, 2014. The $39.0 million increase in our net loss for the year ended December 31, 2015 as compared to the same period in 2014 was primarily due to:

- Increased research and development expenses of $18.0 million primarily resulting from an increase in clinical trial expenses related to the CONVERT study and expenses related to research activities for INS1009, and an increase in manufacturing expenses due to production related to our clinical and research programs; and
- Increased general and administrative expenses of $12.1 million resulting from an increase in compensation expenses, including an increase in headcount, noncash stock-based compensation related to the vesting of certain performance-based stock options, an increase in pre-commercial expenses in Europe and fees and expenses related to the build-out of our European operations and global tax infrastructure.

In addition, there was an $8.4 million decrease in the income tax benefit resulting from the sale of a portion of our New Jersey State NOLs under the Program for cash of $2.0 million and

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$10.4 million in 2015 and 2014, respectively, net of commissions. The $10.4 million benefit in 2014 represents two years of sales of NOLs, one in January 2014 and one in December 2014.

Research and Development Expenses

Research and development expenses for the years ended December 31, 2015 and 2014 were comprised of the following:

	Years Ended December 31,		Increase (decrease)	
	2015	2014	$	%
External Expenses				
Clinical development & research	$ 25,274	$ 12,327	$ 12,947	105.0%
Manufacturing	21,279	16,320	4,959	30.4%
Regulatory and quality assurance	3,051	4,888	(1,837)	(37.6)%
Subtotal external expenses	$ 49,604	$ 33,535	$ 16,069	47.9%
Internal Expenses				
Compensation and related expenses	$ 18,666	$ 17,543	$ 1,123	6.4%
Other internal operating expenses	6,007	5,214	793	15.2%
Subtotal internal expenses	$ 24,673	$ 22,757	$ 1,916	8.4%
Total	$ 74,277	$ 56,292	$ 17,985	31.9%

Research and development expenses increased to $74.3 million during the year ended December 31, 2015 from $56.3 million in the same period in 2014. The $18.0 million increase was primarily due to a $13.0 million increase in external clinical development and research expenses related to the CONVERT study and expenses related to research activities for INS1009. In addition, manufacturing expenses increased $5.0 million primarily due to an increase in production related to our clinical and research programs.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2015 and 2014 were comprised of the following:

	Year Ended December 31,		Increase (decrease)	
	2015	2014	$	%
General & administrative	$ 30,614	$ 23,032	$ 7,582	32.9%
Pre-commercial expenses	12,602	8,041	4,561	56.7%
Total general & administrative expenses	$ 43,216	$ 31,073	$ 12,143	39.1%

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General and administrative expenses increased to $43.2 million during the year ended December 31, 2015 from $31.1 million in the same period in 2014. The $12.1 million increase was primarily due to higher compensation related expenses due to an increase in headcount, an increase in pre-commercial expenses in Europe, a $1.5 million increase in noncash stock-based compensation expense related to the vesting of certain performance based stock options as the recognition criteria was met upon the MAA for ARIKAYCE being accepted for filing by the EMA in February 2015, and fees and expenses related to the build-out of our European operations and global tax infrastructure.

Interest Expense

Interest expense was $2.9 million during the year ended December 31, 2015 as compared to $2.4 million in the same period in 2014. The $0.5 million increase in interest expense in 2015 relates to an increase in our borrowings from Hercules. In December 2014, we entered into a third amendment to the Loan and Security Agreement with Hercules which increased our borrowings by an additional $5.0 million to an aggregate total of $25.0 million.

Income tax benefit

The income tax benefit was $2.0 million and $10.4 million for the years ended December 31, 2015 and 2014, respectively. The income tax benefit recorded for the year ended December 31, 2014 primarily reflects the reversal of a valuation allowance previously recorded against our New Jersey State NOLs that resulted from the sale of a portion of our New Jersey State NOLs under the Program for cash of $10.4 million, net of commissions. The decrease in tax benefit in 2015 was due to timing, as we recognized the full tax benefits of the 2014 sales of NOLs in calendar year 2014, while the 2013 sales of NOLs were recognized in the first quarter of 2014.

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. In recent years, we have funded our operations through public offerings of equity securities and debt financings. We expect to continue to incur losses both in our US and certain international entities, as we plan to fund research and development activities and commercial launch activities.

We will need to raise additional capital to fund our operations, to develop and commercialize ARIKAYCE, to develop INS1007 and INS1009, and to develop, acquire, in-license or co-promote other products that address orphan or rare diseases. We believe we currently have sufficient funds to meet our financial needs for at least the next 12 months. We will opportunistically raise additional capital and may do so through equity or debt financing(s), strategic transactions or otherwise. Such additional funding will 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 2017, we plan to continue to fund further clinical development of ARIKAYCE and INS1007, support efforts to obtain regulatory approvals, and prepare for commercialization of ARIKAYCE. Our cash requirements in 2017 will be impacted by a number of factors, the most significant of which, are expenses related to the CONVERT study and

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pre-commercialization efforts for ARIKAYCE, and to a lesser extent, research and clinical expenses related to INS1007.

On April 6, 2015, we completed an underwritten public offering of 11.5 million shares of our common stock, which included the underwriter's exercise in full of its over-allotment option of 1.5 million shares, at a price to the public of $20.65 per share. Our net proceeds from the sale of the shares, after deducting the underwriter's discount and offering expenses of $14.5 million, were $222.9 million.

Cash Flows

As of December 31, 2016, we had total cash and cash equivalents of $162.6 million, as compared with $282.9 million as of December 31, 2015. The $120.3 million decrease was due primarily to the use of cash in operating activities. Our working capital was $140.4 million as of December 31, 2016 as compared with $265.9 million as of December 31, 2015.

Net cash used in operating activities was $146.7 million and $100.7 million for the years ended December 31, 2016 and 2015, respectively. The net cash used in operating activities during 2016 and 2015 was primarily for the clinical, regulatory and pre-commercial activities related to ARIKAYCE. In addition, in the fourth quarter of 2016, we made a payment of $30 million to AstraZeneca under the AZ License Agreement for INS1007.

Net cash used in investing activities was $4.2 million and $3.5 million for the years ended December 31, 2016 and 2015, respectively. The net cash used in investing activities during 2016 was primarily related to payments for the build out of our headquarters and lab facility in Bridgewater, New Jersey.

Net cash provided by financing activities was $30.7 million and $227.8 million for the years ended December 31, 2016 and 2015, respectively. Net cash provided by financing activities during 2016 included net proceeds of $29.6 million from the issuance of debt as a result of the A&R Loan Agreement with Hercules and proceeds of $1.1 million received from stock option exercises. Net cash provided by financing activities in 2015 included net proceeds of $222.9 million received from the issuance of 11.5 million common shares in April 2015 and proceeds of $5.1 million received from stock option exercises.

Contractual Obligations

On June 29, 2012, we and our domestic subsidiaries, as co-borrowers, entered into a Loan and Security Agreement with Hercules Technology Growth Capital, Inc. (as subsequently amended, the Prior Loan Agreement) under which we borrowed an aggregate of $25.0 million at an interest rate of 9.25%. We paid an "end of term" charge of $390,000 in January of 2016, which was charged to interest expense (and accreted to the debt) using the effective interest method over the life of the Prior Loan Agreement.

On September 30, 2016, we and our domestic subsidiaries, as co-borrowers, entered into the A&R Loan Agreement with Hercules. The A&R Loan Agreement included a total commitment from Hercules of up to $55.0 million, of which $25.0 million was previously outstanding. The amount of borrowings was initially increased by $10.0 million to an aggregate total of $35.0 million on September 30, 2016. An additional $20.0 million was available at our option through June 30, 2017 subject to certain conditions, including the payment of a facility fee of 0.375%. We exercised this option in early October 2016 and borrowed an additional $20.0 million in connection with the upfront

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payment obligation under the AZ License Agreement. The interest rate for the term is floating and is defined as the greater of (i) 9.25% or (ii) 9.25% plus the sum of the US prime rate minus 4.50%, along with a backend fee of 4.15% of the aggregate principal amount outstanding and an aggregate facility fee of $337,500. The interest-only period extends through November 1, 2018, but can be extended up to six months under certain conditions. The maturity date of the loan facility was also extended to October 1, 2020. Pursuant to the A&R Loan Agreement, we are required to have a consolidated minimum cash liquidity in an amount no less than $25.0 million. Such requirement terminates upon the earlier of the date by which we complete an equity financing with at least $75.0 million in proceeds or the date we generate and announce data from the CONVERT study in a manner that could support an NDA filing. In addition, pursuant to the A&R Loan Agreement, Hercules has the right to participate, in an aggregate amount of up to $2.0 million, in a subsequent private financing that involves the issuance of our equity securities.

In connection with the A&R 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 A&R Loan Agreement is subject to penalty. The backend fee of 4.15% on the aggregate outstanding principal balance will be charged to interest expense (and accreted to the debt) using the effective interest method over the original life of the A&R Loan Agreement. 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 A&R Loan Agreement.

We have an operating lease for office and laboratory space located in Bridgewater, NJ, our corporate headquarters, for which the initial lease term expires in November 2019. Future minimum rental payments under this lease total approximately $3.0 million. In July 2016, we signed an operating lease for additional laboratory space located in Bridgewater, NJ for which the initial lease term expires in September 2021. Future minimum rental payments under this lease are $2.1 million.

In September 2015, we entered into a Commercial Fill/Finish Services Agreement (the Fill/Finish Agreement) with Ajinomoto Althea, Inc., a Delaware corporation (Althea), for Althea to produce, on a non-exclusive basis, ARIKAYCE in finished dosage form. Under the Fill/Finish Agreement, we are obligated to pay a minimum of $2.7 million for the batches of ARIKAYCE produced each calendar year during the term of the Fill/Finish Agreement. The Fill/Finish Agreement was effective as of January 1, 2015, and had an initial term that was to end on December 31, 2017. In 2016, we signed an extension of the agreement through December 31, 2019 and it may be extended for additional two year periods upon mutual written agreement of the Company and Althea at least one year prior to the expiration of its then-current term.

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As of December 31, 2016, future payments under our long-term debt agreements, minimum future payments under non-cancellable operating leases and minimum future payment obligations are as follows:

	As of December 31, 2016 Payments Due By Period				
	Total	Less than 1 year	1 - 3 Years	4 - 5 Years	After 5 Years
	(In thousands)				
Debt obligations					
Debt maturities	$ 55,000	$ -	$ 24,024	$ 30,976	$ -
Contractual interest	18,332	5,158	9,118	4,056	-
Operating leases	5,219	1,445	2,870	904	-
Purchase obligations	8,100	2,700	5,400	-	-
Total contractual obligations	$ 86,651	$ 9,303	$ 41,412	$ 35,936	$ -

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 the 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 in the mid-single digits on commercial net sales of ARIKAYCE pursuant to the licensing agreement, subject to certain specified annual minimum royalties. 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 LAI. The PARI Agreement has an initial term of fifteen years from the first commercial sale of ARIKAYCE pursuant to the licensing agreement (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.

In 2004 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 patients with 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 five years of the drug commercialization, we would owe an additional $3.9 million in additional payments. Since there is significant development and regulatory risk associated with ARIKAYCE, including with respect to the CF indication, we have not accrued these obligations.

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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 collaborated with Therapure to construct a production area for the manufacture of ARIKAYCE in Therapure's existing manufacturing facility in Canada. 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. Under the agreement, we are obligated to pay certain minimum amounts for the batches of ARIKAYCE produced each calendar year.

In December 2014, we entered into a services agreement with SynteractHCR, Inc. (Synteract) pursuant to which we retained Synteract to perform implementation and management services in connection with the 212 study. We anticipate that aggregate costs relating to all work orders for the 212 study will be approximately $45 million over the period of the study. In April 2015, we entered into a work order with Synteract to perform implementation and management services for the 312 study. We anticipate that aggregate costs relating to all work orders for the 312 study will be approximately $25 million over the period of the study.

In October 2016, we entered into the AZ License Agreement. Pursuant to the terms of the AZ License Agreement, AstraZeneca granted to us exclusive global rights for the purpose of developing and commercializing AZD7986 (which we renamed INS1007). In consideration of the licenses and other rights granted by AstraZeneca, we made an upfront payment of $30.0 million, which was included as research and development expense in the fourth quarter of 2016. We are obligated to make a series of contingent milestone payments totaling up to an additional $85.0 million upon the achievement of clinical development and regulatory filing milestones. If we elect to develop INS1007 for a second indication, we will be obligated to make an additional series of contingent milestone payments totaling up to $42.5 million. No additional milestone payments are due for any indications beyond the first and second indications. In addition, we will pay AstraZeneca tiered royalties ranging from a high single-digit to mid-teen on net sales of any approved product based on INS1007 and one additional payment of $35.0 million upon the first achievement of $1 billion in annual net sales. The AZ License Agreement provides AstraZeneca with the option to negotiate a future agreement with us for commercialization of INS1007 in chronic obstructive pulmonary disease or asthma.

Future Funding Requirements

To date, we have not generated material revenue from ARIKAYCE, and we do not know when, or if, we will generate such revenue. We do not expect to generate such revenue unless or until we obtain marketing approval of, secure reimbursement for, and commercialize, ARIKAYCE. We will need to raise additional capital to fund our operations, to develop and commercialize ARIKAYCE, to develop INS1007 and 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, defending, and enforcing patent claims;
- the timing and cost of our anticipated clinical trials, including INS1007 and the related milestone payments due to AstraZeneca;

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- 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.

In April 2015, we generated net proceeds of $222.9 million from the issuance of 11.5 million shares of common stock. On September 30, 2016, the total committed amount under the A&R Loan Agreement with Hercules was increased to $55.0 million, $25.0 million of which was previously outstanding. During the fourth quarter of 2016, we drew down the remaining commitment. We believe we currently have sufficient funds to meet our financial needs for the next 12 months. However, our business strategy will require us to raise additional capital at any time through equity or debt financing(s), strategic transactions or otherwise. Such additional funding will 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.

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, stock-based compensation, identifiable intangible assets, 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.*

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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, including the medical devices for drug delivery, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. In addition, research and development expenses include payments to third parties for the license rights to products in development (prior to marketing approval). Our expenses related to manufacturing our drug candidate and medical devices for clinical study are primarily related to activities at contract manufacturing organizations that manufacture ARIKAYCE, and to a lesser extent, our other clinical product requirements. 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.

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.

The following table summarizes the assumptions used in determining the fair value of stock options granted during the years ended December 31, 2016, 2015 and 2014:

	2016	2015	2014
Volatility	74% - 77%	78% - 82%	83% - 86%
Risk-free interest rate	1.00% - 1.90%	1.31% - 1.75%	1.46% - 1.83%
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, 2016, 2015 and 2014, the volatility factor was based on our historical volatility since the closing of our merger with Transave, Inc. in December 2010. The expected life was determined using the simplified method as described in Accounting Standards Codification 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 in December 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 Adopted

In August 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2014-15, *Presentation of Financial Statements Going Concern: Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern,* which requires management to evaluate whether there is substantial doubt about the entity's ability to continue as a going concern and, if so, provide certain footnote disclosures. This ASU was effective for the annual period ended December 31, 2016, and interim reporting periods thereafter. The adoption of this standard did not have an impact on our consolidated financial statements and related footnote disclosures.

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In November 2015, the FASB issued ASU 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes*, which updated and simplified the presentation of deferred income taxes. Current generally accepted accounting principles require an entity to separate deferred income tax liabilities and assets into current and noncurrent amounts in a classified statement of financial position. To simplify the presentation of deferred income taxes, the amendments in this update require that deferred tax liabilities and assets be classified as noncurrent in a classified statement of financial position. The amendments in this update are effective for financial statements issued for annual periods beginning after December 15, 2016 and interim periods within those annual periods. Earlier application was permitted and we adopted the update effective with our annual reporting period ended December 31, 2015. The adoption of this update did not have a significant impact on our consolidated financial statements.

Recent Accounting Pronouncements Not Yet Adopted

In May 2014, the FASB issued ASU 2014-09, *Revenue from Contracts with Customers (Topic 606)* which amended the existing accounting standards for revenue recognition. ASU 2014-09 establishes principles for recognizing revenue upon the transfer of promised goods or services to customers, in an amount that reflects the expected consideration received in exchange for those goods or services. In July 2015, the FASB deferred the effective date for annual reporting periods beginning after December 15, 2017. We expect to adopt ASU 2014-09 in the first quarter of 2018 and the impact of adoption will not be material to our consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)* in order to increase transparency and comparability among organizations by recognizing lease assets and lease liabilities on the balance sheet for those leases classified as operating leases under previous GAAP. ASU 2016-02 requires that a lessee should recognize a liability to make lease payments (the lease liability) and a right-of-use asset representing its right to use the underlying asset for the lease term on the balance sheet. ASU 2016-02 is effective for fiscal years beginning after December 15, 2018 (including interim periods within those periods) using a modified retrospective approach and early adoption is permitted. We expect to adopt ASU 2016-02 in the first quarter of 2019 and are in the process of evaluating the impact of adoption on our consolidated financial statements.

In March 2016, the FASB issued ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting*, which amends ASC Topic 718, *Compensation Stock Compensation*. ASU 2016-09 simplifies several aspects of the accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, and classification on the statement of cash flows. ASU 2016-09 is effective for fiscal years beginning after December 15, 2016, and interim periods within those fiscal years. We will adopt ASU 2016-09 in the first quarter of 2017 and we are in the process of evaluating the impact of adoption on our consolidated financial statements.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As of December 31, 2016, 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, 2016, we had $55.0 million of fixed rate borrowings bearing interest at 9.25% outstanding under the A&R Loan Agreement with Hercules. If a 10% change in interest rates was to have occurred on December 31, 2016, 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.

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The majority of our business is conducted in US dollars. However, we do conduct certain transactions in other currencies, including Euros, British Pounds and Japanese Yen. Fluctuations in foreign currency exchange rates do not materially affect our results of operations. During 2016, 2015 and 2014, 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, 2016. 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, 2016, our Chief Executive Officer and Chief Financial Officer have concluded that our disclosure controls and procedures are effective at the reasonable assurance level.

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 US 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.

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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, 2016, 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, 2016.

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

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by Item 10 of Form 10-K is 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 2017 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

ITEM 11. EXECUTIVE COMPENSATION

The information required by Item 11 of Form 10-K is 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 *Director Compensation* in our definitive proxy statement for our 2017 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

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

The information required by Item 12 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Compensation Discussion and Analysis*, *Security Ownership of Certain Beneficial Owners, Directors and Management* in our definitive proxy statement for our 2017 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

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ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS AND DIRECTOR INDEPENDENCE

The information required by Item 13 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Election of Class II Directors* and *Certain Relationships and Related Transactions* in our definitive proxy statement for our 2017 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required by Item 14 of Form 10-K is incorporated by reference from the discussion responsive thereto under the caption *Corporate Governance* and *Ratification of Independent Registered Public Accounting Firm* in our definitive proxy statement for our 2017 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report.

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 89:

(i)

Reports of Independent Registered Public Accounting Firm

(ii)

Consolidated Balance Sheets as of December 31, 2016 and 2015

(iii)

Consolidated Statements of Comprehensive Loss for the Years Ended December 31, 2016, 2015 and 2014

(iv)

Consolidated Statements of Shareholders' Equity for the Years Ended December 31, 2016, 2015 and 2014

(v)

Consolidated Statements of Cash Flows for the Years Ended December 31, 2016, 2015 and 2014

(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.

ITEM 16. FORM 10-K SUMMARY

Not applicable.

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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 23, 2017.

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 23, 2017.

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

/s/ MELVIN SHAROKY, M.D.

Director

Melvin Sharoky, M.D.

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Report of Independent Registered Public Accounting Firm

The Board of Directors and Shareholders of Insmed Incorporated

We have audited the accompanying consolidated balance sheets of Insmed Incorporated as of December 31, 2016 and 2015, and the related consolidated statements of comprehensive loss, shareholders' equity and cash flows for each of the three years in the period ended December 31, 2016. 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, 2016 and 2015, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, 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, 2016, 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 23, 2017 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Iselin, New Jersey
February 23, 2017

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Report of Independent Registered Public Accounting Firm

The Board of Directors and Shareholders of Insmed Incorporated

We have audited Insmed Incorporated's internal control over financial reporting as of December 31, 2016, 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, 2016, 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, 2016 and 2015, and the related consolidated statements of comprehensive loss, shareholders' equity and cash flows for each of the three years in the period ended December 31, 2016 and our report dated February 23, 2017 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Iselin, New Jersey
February 23, 2017

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

	As of December 31,	
	2016	**2015**
Assets		
Current assets:		
Cash and cash equivalents	$ 162,591	$ 282,876
Prepaid expenses and other current assets	5,816	5,242
Total current assets	168,407	288,118
In-process research and development	58,200	58,200
Fixed assets, net	10,020	8,092
Other assets	1,329	2,146
Total assets	$ 237,956	$ 356,556
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 10,439	$ 7,468
Accrued expenses	16,822	10,995
Other current liabilities	728	683
Current portion of long-term debt	-	3,113
Total current liabilities	27,989	22,259
Long-term liabilities:		
Other long-term liabilities	693	572
Debt, long-term	54,791	22,027
Total liabilities	83,473	44,858
Common stock, $0.01 par value; 500,000,000 authorized shares, 62,019,889 and 61,813,995 issued and outstanding shares at December 31, 2016 and December 31, 2015, respectively	620	618
Additional paid-in capital	919,164	900,043
Accumulated deficit	(765,236)	(588,963)
Accumulated other comprehensive loss	(65)	-
Total shareholders' equity	154,483	311,698
Total liabilities and shareholders' equity	$ 237,956	$ 356,556

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,		
	2016	**2015**	**2014**
Revenues	$ -	$ -	$ -
Operating expenses:			
Research and development	122,721	74,277	56,292
General and administrative	50,679	43,216	31,073
Total operating expenses	173,400	117,493	87,365
Operating loss	(173,400)	(117,493)	(87,365)
Investment income	604	261	58
Interest expense	(3,498)	(2,889)	(2,415)
Other income (expense), net	119	(33)	141
Loss before income taxes	(176,175)	(120,154)	(89,581)
Income tax provision (benefit)	98	(1,971)	(10,422)
Net loss	$ (176,273)	$ (118,183)	$ (79,159)
Basic and diluted net loss per share	$ (2.85)	$ (2.02)	$ (1.84)
Weighted average basic and diluted common shares outstanding	61,892	58,633	43,095
Net loss	$ (176,273)	$ (118,183)	$ (79,159)
Other comprehensive loss:			
Foreign currency translation loss	(65)	-	-
Total comprehensive loss	$ (176,338)	$ (118,183)	$ (79,159)

See accompanying notes to audited consolidated financial statements

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

	Common Stock		Additional Paid-in		Accumulated Other	
	Shares	Amount	Capital	Accumulated Deficit	Comprehensive Loss	Total
Balance at January 1, 2014	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
Comprehensive loss:						
Net loss				(118,183)		(118,183)
Exercise of stock options	481	5	5,107			5,112
Net proceeds from issuance of common stock	11,500	115	222,827			222,942
Issuance of common stock for vesting of RSUs	27					-
Stock compensation expense			15,590			15,590
Balance at December 31, 2015	61,814	$ 618	$ 900,043	$ (588,963)	$ -	$ 311,698
Comprehensive loss:						
Net loss				(176,273)		(176,273)
Other comprehensive loss					(65)	(65)
Exercise of stock options	162	2	1,082			1,084
Issuance of common stock for vesting of RSUs	44					-
Stock compensation expense			18,039			18,039
Balance at December 31, 2016	62,020	$ 620	$ 919,164	$ (765,236)	$ (65)	$ 154,483

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,		
	2016	**2015**	**2014**
Operating activities			
Net loss	$ (176,273)	$ (118,183)	$ (79,159)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	2,438	1,982	1,073
Stock based compensation expense	18,039	15,590	11,328
Loss on sale of assets, net	-	-	9
Amortization of debt issuance costs	281	458	390
Accrual of the end of term charge on the debt	171	76	110
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	191	(1,484)	(2,972)
Accounts payable	2,767	(1,781)	3,312
Accrued expenses and other	5,678	2,642	1,493
Net cash used in operating activities	(146,708)	(100,700)	(64,416)
Investing activities			
Purchase of fixed assets	(4,200)	(3,454)	(5,351)
Proceeds from sale of asset	-	-	10
Net cash used in investing activities	(4,200)	(3,454)	(5,341)
Financing activities			
Payments on capital lease obligations	-	-	(64)
Proceeds from issuance of debt	30,000	-	5,000
Proceeds from issuance of common stock	-	222,942	109,013
Proceeds from exercise of stock options	1,084	5,112	1,390
Payment of debt issuance costs	(411)	(250)	(250)
Net cash provided by financing activities	30,673	227,804	115,089
Effect of exchange rates on cash and cash equivalents	(50)	-	-
Net (decrease) increase in cash and cash equivalents	(120,285)	123,650	45,332
Cash and cash equivalents at beginning of period	282,876	159,226	113,894
Cash and cash equivalents at end of period	$ 162,591	$ 282,876	$ 159,226
Supplemental disclosures of cash flow information:			
Cash paid for interest	$ 3,608	$ 2,948	$ 1,803
Cash (paid) received for taxes, net	$ (85)	$ 3,008	$ 9,429

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 global biopharmaceutical company focused on the unmet needs of patients with rare diseases. The Company's lead product candidate is ARIKAYCE, or liposomal amikacin for inhalation (LAI), which is in late-stage development for adult patients with treatment refractory nontuberculous mycobacteria (NTM) lung disease, a rare and often chronic infection that is capable of causing irreversible lung damage and which can be fatal. The Company's earlier clinical-stage pipeline includes INS1007, a novel oral reversible inhibitor of dipeptidyl peptidase 1, and INS1009, an inhaled treprostinil prodrug nanoparticle formulation.

The Company has funded its operations, in recent years, through public offerings of equity securities and debt financings. The Company expects to continue to incur losses in order to fund research and development activities for its clinical programs and commercial launch activities for ARIKAYCE. The Company will need to raise additional capital to fund operations, to develop and commercialize ARIKAYCE, to develop INS1007 and INS1009, and to develop, acquire, in-license or co-promote other products that address orphan or rare diseases. The Company believes it currently has sufficient funds to meet its financial needs for at least the next 12 months.

The Company was incorporated in the Commonwealth of Virginia on November 29, 1999 and its principal executive offices are located in Bridgewater, New Jersey. The Company has legal entities in the United States (US), Ireland, Germany, France, the United Kingdom (UK) and the Netherlands.

Basis of Presentation The consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries, Insmed Limited, Celtrix Pharmaceuticals, Inc., Insmed Holdings Limited, Insmed Ireland Limited, Insmed France SAS, Insmed Germany GmbH and Insmed Netherlands B.V. All intercompany transactions and balances 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 affected 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 and cash equivalents. 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

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

computer equipment. Estimated useful lives of seven years are used for laboratory equipment, office equipment, manufacturing equipment and furniture and fixtures. Leasehold improvements are amortized over the shorter of the 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. 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. A market based valuation approach was not considered given a lack of revenues and profits for the Company.

Debt Issuance Costs Debt issuance costs are amortized to interest expense using the effective interest rate method over the term of the debt. Debt issuance costs paid to the lender and third parties are reflected as a discount to the debt in the consolidated balance sheets. Unamortized debt issuance costs associated with extinguished debt are expensed in the period of the extinguishment.

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

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

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.
- 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 is 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, 2016 and December 31, 2015 were its cash and cash equivalents of $162.6 million and $282.9 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 2016 and 2015.

As of December 31, 2016 and 2015, the Company held no securities that were in an unrealized loss or gain position.

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.

Foreign Currency The Company has operations in the US, Ireland, Germany, France, the UK and the Netherlands. The results of its non-US dollar based functional currency operations are translated to US dollars at the average exchange rates during the period. Assets and liabilities are translated at the exchange rate prevailing at the balance sheet date. Equity is translated at the

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

prevailing exchange rate at the date of the equity transaction. Translation adjustments are included in shareholders' equity, as a component of other comprehensive loss.

The Company realizes foreign currency transaction gains (losses) in the normal course of business based on movements in the applicable exchange rates. These gains (losses) are included as a component of other income (expense), net.

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.

The Company sources its raw materials from single suppliers. 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 In 2015, the French National Agency for Medicines and Health Products Safety (ANSM) granted LAI a Temporary Authorizations for Use (Autorisation Temporaire d'Utilisation or ATU). Pursuant to this program, the Company shipped product to pharmacies after receiving requests from physicians for patients in France. For the years ended December 31, 2016 and 2015, the revenue recorded was immaterial and is included as a component of other income (expense), net. The Company is initiating expanded access programs (EAPs) in other select territories in Europe, some of which may be fully reimbursed. EAPs are intended to make products available on a named patient basis before they are commercially available in accordance with local regulations. The Company did not recognize any revenue in 2014.

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.

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. In addition, research and development expenses include payments to third parties for the license rights to products in development (prior to marketing approval). 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, INS1007, and INS1009 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

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

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 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.

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 had no uncertain tax positions as of December 31, 2016 and 2015 that qualified for either recognition or disclosure in the consolidated financial statements.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

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 tax provision (benefit) 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 shareholders 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. Potentially dilutive securities from stock options and restricted stock units 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 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, 2016, 2015 and 2014.

	Years Ended December 31,		
	2016	2015	2014
	(in thousands, except per share amounts)		
Numerator:			
Net loss	$ (176,273)	$ (118,183)	$ (79,159)
Denominator:			
Weighted average common shares used in calculation of basic net loss per share:	61,892	58,633	43,095
Effect of dilutive securities:			
Common stock options	-	-	-
Restricted stock and restricted stock units	-	-	-
Weighted average common shares outstanding used in calculation of diluted net loss per share	61,892	58,633	43,095
Net loss per share:			
Basic and Diluted	$ (2.85)	$ (2.02)	$ (1.84)

The following potentially dilutive securities have been excluded from the computations of diluted weighted-average common shares outstanding as of December 31, 2016, 2015 and 2014 as their effect would have been anti-dilutive (in thousands).

	2016	2015	2014
Stock options to purchase common stock	7,117	5,274	4,400
Restricted stock and restricted stock units	89	44	21

Segment Information The Company currently operates in one business segment, which is the development and commercialization of therapies for patients with rare diseases. A single management team that reports to the Chief Executive Officer comprehensively manages the entire business. The

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

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.

New Accounting Pronouncements (Adopted) In August 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2014-15, *Presentation of Financial Statements Going Concern: Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern,* which requires management to evaluate whether there is substantial doubt about the entity's ability to continue as a going concern and, if so, provide certain footnote disclosures. This ASU was effective for the annual period ended December 31, 2016, and interim reporting periods thereafter. The adoption of this standard did not have an impact on the Company's consolidated financial statements and related footnote disclosures.

In November 2015, the FASB issued ASU 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes*, which updated and simplified the presentation of deferred income taxes. Current generally accepted accounting principles require an entity to separate deferred income tax liabilities and assets into current and noncurrent amounts in a classified statement of financial position. To simplify the presentation of deferred income taxes, the amendments in this update require that deferred tax liabilities and assets be classified as noncurrent in a classified statement of financial position. The amendments in this update are effective for financial statements issued for annual periods beginning after December 15, 2016 and interim periods within those annual periods. Earlier application was permitted and the Company adopted the update effective with its annual reporting period ended December 31, 2015. The adoption of this update did not have a significant impact on the Company's consolidated financial statements.

New Accounting Pronouncements (Not Yet Adopted) In May 2014, the FASB issued ASU 2014-09*Revenue from Contracts with Customers (Topic 606)* which amended the existing accounting standards for revenue recognition. ASU 2014-09 establishes principles for recognizing revenue upon the transfer of promised goods or services to customers, in an amount that reflects the expected consideration received in exchange for those goods or services. In July 2015, the FASB deferred the effective date for annual reporting periods beginning after December 15, 2017. The Company expects to adopt ASU 2014-09 in the first quarter of 2018 and the impact of adoption will not be material to its consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)* in order to increase transparency and comparability among organizations by recognizing lease assets and lease liabilities on the balance sheet for those leases classified as operating leases under previous GAAP. ASU 2016-02 requires that a lessee should recognize a liability to make lease payments (the lease liability) and a right-of-use asset representing its right to use the underlying asset for the lease term on the balance sheet. ASU 2016-02 is effective for fiscal years beginning after December 15, 2018 (including interim periods within those periods) using a modified retrospective approach and early adoption is permitted. The Company expects to adopt ASU 2016-02 in the first quarter of 2019 and is in the process of evaluating the impact of adoption on its consolidated financial statements.

In March 2016, the FASB issued ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting*, which amends ASC Topic 718, *Compensation Stock Compensation*. ASU 2016-09 simplifies

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

2. Summary of Significant Accounting Policies (Continued)

several aspects of the accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, and classification on the statement of cash flows. ASU 2016-09 is effective for fiscal years beginning after December 15, 2016, and interim periods within those fiscal years. The Company will adopt ASU 2016-09 in the first quarter of 2017 and is in the process of evaluating the impact of adoption on its consolidated financial statements.

3. Accrued Expenses

Accrued expenses consist of the following:

	As of December 31,	
	2016	2015
	(in thousands)	
Accrued clinical trial expenses	$ 7,071	$ 4,331
Accrued compensation	6,937	4,302
Accrued professional fees	1,604	1,202
Accrued technical operation expenses	591	702
Accrued interest payable	438	199
Other accrued expenses	181	259
	$ 16,822	$ 10,995

4. Identifiable Intangible Assets

The Company's only identifiable intangible asset was in-process research and development (IPRD) related to ARIKAYCE as of December 31, 2016 and 2015. The total intangible IPRD asset was $58.2 million as of December 31, 2016 and 2015, which resulted from the initial amount recorded at the time of the Company's merger with Transave in 2010 and subsequent adjustments in the value. 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 will not be amortized until commercialization. If commercialization occurs, intangible assets will be amortized over their estimated useful lives. As of December 31, 2016, the Company did not identify any indicators of impairment of its in-process research and development intangible assets and the implied value of the intangible assets was more than 100% greater than the book value.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

5. Fixed Assets, net

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

Asset Description	Estimated Useful Life (years)	As of December 31, 2016	2015
		(in thousands)	
Lab equipment	7	$ 5,662	$ 3,957
Furniture and fixtures	7	1,903	1,127
Computer hardware and software	3 - 5	2,251	1,969
Office equipment	7	65	65
Manufacturing equipment	7	1,148	980
Leasehold improvements	lease term	6,735	5,300
		17,764	13,398
Less accumulated depreciation		(7,744)	(5,306)
Fixed assets, net		$ 10,020	$ 8,092

Depreciation expense was $2.4 million, $2.0 million and $1.1 million for the years ended December 31, 2016, 2015 and 2014, respectively.

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. (as subsequently amended, the Prior Loan Agreement) under which the Company borrowed an aggregate of $25.0 million at an interest rate of 9.25%. The Company was required to pay an "end of term" charge of $390,000 in January of 2016, which was charged to interest expense (and accreted to the debt) using the effective interest method over the life of the Prior Loan Agreement.

On September 30, 2016, the Company and its domestic subsidiaries, as co-borrowers, entered into an Amended and Restated Loan and Security Agreement (the A&R Loan Agreement) with Hercules Capital, Inc. (Hercules). The A&R Loan Agreement included a total commitment from Hercules of up to $55.0 million, of which $25.0 million was previously outstanding. The amount of borrowings was increased by $10.0 million to an aggregate total of $35.0 million on September 30, 2016. An additional $20.0 million was available at the Company's option through June 30, 2017 subject to certain conditions, including the payment of a facility fee of 0.375%. The Company exercised this option in early October 2016 and borrowed an additional $20.0 million in connection with its upfront payment obligation under the License Agreement with AstraZeneca (see *Note 10*). The interest rate for the term is floating and is defined as the greater of (i) 9.25% or (ii) 9.25% plus the sum of the US prime rate minus 4.50%, along with a backend fee of 4.15% of the aggregate principal amount outstanding and an aggregate facility fee of $337,500. The interest-only period extends through

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

6. Debt (Continued)

November 1, 2018, but can be extended up to six months under certain conditions. The maturity date of the loan facility was also extended to October 1, 2020. Pursuant to the A&R Loan Agreement, the Company is required to have consolidated minimum cash liquidity in an amount no less than $25.0 million. Such requirement terminates upon the earlier of the date by which the Company completes an equity financing with at least $75.0 million in proceeds or the date the Company generates and announces data from the CONVERT study in a manner that could support an NDA filing. In addition, pursuant to the A&R Loan Agreement, Hercules has the right to participate, in an aggregate amount of up to $2.0 million, in a subsequent private financing that involves the issuance of our equity securities.

In connection with the A&R Loan Agreement, the Company granted Hercules a first position lien on all of the Company's assets, excluding intellectual property. Prepayment of the loans made pursuant to the A&R Loan Agreement is subject to penalty. The backend fee of 4.15% on the aggregate outstanding principal balance will be charged to interest expense (and accreted to the debt) using the effective interest method over the original life of the A&R Loan Agreement. Debt issuance fees paid to Hercules 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 A&R Loan Agreement.

The A&R Loan Agreement also contains representations and warranties by the Company and the lender and indemnification provisions in favor of the lender and customary covenants (including limitations on other indebtedness, liens, acquisitions, investments and dividends, and a minimum liquidity covenant), 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 A&R Loan Agreement.

The following table presents the components of the Company's debt balance as of December 31, 2016 (in thousands):

Debt:		
Note payable under A&R Loan Agreement	$	55,000
Accretion of end of term charge		171
Issuance fees paid to lender		(380)
Current portion of long-term debt		-
Long-term debt	$	54,791

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

6. Debt (Continued)

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

Year Ending in December 31:		
2017	$	-
2018		3,271
2019		20,753
2020		30,976
	$	55,000

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, 2016 and 2015, the fair value of the Company's debt approximates the carrying amount.

7. Shareholders' Equity

Common Stock As of December 31, 2016, the Company had 500,000,000 shares of common stock authorized with a par value of $0.01 and 62,019,889 shares of common stock issued and outstanding. In addition, as of December 31, 2016, the Company had reserved 7,116,706 shares of common stock for issuance upon the exercise of outstanding common stock options and 89,194 shares of common stock for issuance upon the vesting of restricted stock units.

In April 2015, the Company completed an underwritten public offering of 11,500,000 shares of the Company's common stock, which included the underwriter's exercise in full of its over-allotment option of 1,500,000 shares, at a price to the public of $20.65 per share. The Company's net proceeds from the sale of the shares, after deducting the underwriter's discount and offering expenses of $14.5 million, were $222.9 million.

In August 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.

In December 2014, in connection with the Third Amendment to the Prior 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 Securities Act) and may not be offered or sold in the US in the absence of an effective registration statement or exemption from the registration requirements under the Securities Act. The issuance of the securities in this transaction were exempt from registration under Section 4(2) of the Securities Act.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

7. Shareholders' Equity (Continued)

Preferred Stock As of December 31, 2016 and 2015, 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.

8. Stock-Based Compensation

The Company's current equity compensation plan, the 2015 Incentive Plan, was approved by shareholders at the Company's 2015 Annual Meeting of Shareholders. The 2015 Incentive Plan is administered by the Compensation Committee and the Board of Directors of the Company. Under the terms of the 2015 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 Company has 5,000,000 shares of common stock authorized for issuance under the 2015 Incentive Plan and, as of December 31, 2016, there were 2,266,465 shares remaining for future grants (or issuances) of stock options, stock appreciation rights, restricted stock, restricted stock units and incentive bonuses thereunder. The 2015 Incentive Plan will terminate on April 9, 2025 unless it is extended or terminated earlier pursuant to its terms. In addition, from time to time, the Company makes inducement grants of stock options. These awards are made pursuant to the NASDAQ inducement grant exception as a component of new hires' employment compensation. Inducement stock options granted to new employees during the years ended December 31, 2016 and 2015 were 88,060 and 227,000, respectively.

Stock Options The Company calculates the fair value of stock options granted using the Black-Scholes valuation model. The following table summarizes the grant date fair value and assumptions used in determining the fair value of all stock options granted, including grants of inducement options, during the years ended December 31, 2016, 2015 and 2014.

	2016	2015	2014
Volatility	74% - 77%	78% - 82%	83% - 86%
Risk-free interest rate	1.00% - 1.90%	1.31% - 1.75%	1.46% - 1.83%
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	$8.77	$14.20	$11.74

For the years ended December 31, 2016, 2015 and 2014, the volatility factor was based on the Company's historical volatility since the closing of the merger with Transave in December 2010. The expected option term 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, and this is the basis for future forfeiture expectations.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

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 a result of the Marketing Authorization Application (MAA) acceptance for ARIKAYCE, which was received from the European Medicines Agency (EMA) in February 2015, the vesting of performance options totaling $1.5 million were recorded as non-cash compensation expense in the first quarter of 2015. As of December 31, 2016, the Company had performance options totaling 158,334 shares outstanding.

The following table summarizes stock option activity for stock options granted for the years ended December 31, 2016, 2015 and 2014 as follows:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life in Years	Aggregate Intrinsic Value (in '000)
Options outstanding at January 1, 2014	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		
Vested and expected to vest at December 31, 2014	3,891,511	10.32		
Exercisable at December 31, 2014	1,235,710	6.90		
Options outstanding at December 31, 2014	4,400,106	$ 10.59		
Granted	1,902,850	20.45		
Exercised	(481,140)	10.62		
Forfeited and expired	(548,094)	15.43		
Options outstanding at December 31, 2015	5,273,722	$ 13.64		
Vested and expected to vest at December 31, 2015	5,059,645	13.46		
Exercisable at December 31, 2015	1,991,141	8.70		

Options outstanding at December 31, 2015	5,273,722	$	13.64			
Granted	2,532,675		12.96			
Exercised	(162,340)		6.68			
Forfeited and expired	(527,351)		17.08			
Options outstanding at December 31, 2016	7,116,706	$	13.30	7.71	$	16,293
Vested and expected to vest at December 31, 2016	6,850,658	$	13.25	7.67	$	16,009
Exercisable at December 31, 2016	3,113,998	$	11.28	6.58	$	12,368

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

The total intrinsic value of stock options exercised during the years ended December 31, 2016, 2015 and 2014 was $1.0 million, $4.7 million and $2.5 million, respectively.

As of December 31, 2016, there was $26.8 million of unrecognized compensation expense related to unvested stock options, which is expected to be recognized over a weighted average period of 2.7 years. Included above in unrecognized compensation expense was $1.2 million related to 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, 2016:

	Outstanding as of December 31, 2016					Exercisable as of December 31, 2016	
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	$ 3.03	124,482	4.94	$ 3.03	124,482	$ 3.03	
$ 3.29	$ 3.40	718,214	5.68	$ 3.40	718,214	$ 3.40	
$ 3.60	$ 6.90	519,003	5.91	$ 5.94	444,282	$ 5.78	
$ 6.96	$ 10.85	1,193,996	9.27	$ 10.75	16,863	$ 7.44	
$ 11.14	$ 12.44	779,695	7.19	$ 12.01	413,477	$ 12.08	
$ 12.45	$ 14.24	842,127	7.47	$ 13.27	481,611	$ 13.35	
$ 14.32	$ 16.09	598,364	8.06	$ 15.68	214,516	$ 15.82	
$ 16.16	$ 16.16	739,150	8.98	$ 16.16	-	-	
$ 16.19	$ 20.92	727,250	7.56	$ 19.42	368,638	$ 19.56	
$ 21.20	$ 27.38	874,425	8.24	$ 22.82	331,915	$ 22.83	

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 share of RS vests upon and each 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 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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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

8. Stock-Based Compensation (Continued)

The following table summarizes RSU awards granted during the years ended December 31, 2016, 2015 and 2014:

	Number of RSUs	Weighted Average Grant Price
Outstanding at January 1, 2014	92,641	$ 6.27
Granted	20,502	19.47
Released	(92,641)	6.27
Forfeited	-	-
Outstanding at December 31, 2014	20,502	$ 19.47
Granted	49,776	16.07
Released	(26,724)	18.68
Forfeited	-	-
Outstanding at December 31, 2015	43,554	$ 16.07
Granted	89,194	10.85
Released	(43,554)	16.07
Forfeited	-	-
Outstanding at December 31, 2016	89,194	$ 10.85

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, 2016, 2015 and 2014:

	2016	2015	2014
		(in millions)	
Research and development expenses	$ 6.2	$ 4.0	$ 4.5
General and administrative expenses	11.8	11.6	6.8
Total(1)	$ 18.0	$ 15.6	$ 11.3

(1) Includes $1.7 million, $2.3 million and $2.4 million for the years ended December 31, 2016, 2015 and 2014, respectively, for the remeasurement of certain stock options and RSUs that occurred during May 2013.

9. Income Taxes

The income tax provision (benefit) was $0.1 million, $(2.0) million and $(10.4) million and the effective rates were approximately 0%, 2% and 12% for the years ended December 31, 2016, 2015 and 2014, respectively. The income tax provision for the year ended December 31, 2016 reflected current income tax expense recorded as a result of the taxable income in certain of the Company's subsidiaries

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

9. Income Taxes (Continued)

in Europe. The income tax benefit recorded and the effective tax rates for the years ended December 31, 2015 and 2014 primarily reflected the reversal of valuation allowances previously recorded against the Company's New Jersey State net operating losses (NOLs) that resulted from the Company's sale of $24.3 million and $110.5 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 $2.0 million and $10.4 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. In 2015, the Company reached the lifetime maximum cap of NOLs that can be sold to the State of New Jersey. Therefore, the Company did not receive any cash proceeds from the Program in 2016 and will no longer receive cash proceeds from the Program in the future.

The Company is subject to US federal and state income taxes and the statute of limitations for tax audit is open for the federal tax returns for the years ended 2013 and later, and is generally open for certain states for the years 2012 and later. The Company's US federal tax return for the year ended December 31, 2013 is currently under audit by the Internal Revenue Service. The Company has incurred net operating losses since inception, except for the year ended December 31, 2009. 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, 2016 and 2015, 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 12 months.

For the years ended December 31, 2016 and 2015, the Company was also subject to foreign income taxes as a result of legal entities established for activities in Europe. The Company's loss before income taxes in the US and globally was as follows (in thousands):

	Years ended December 31,		
	2016	**2015**	**2014**
US	$ (140,354)	$ (100,278)	$ (89,581)
Foreign	(35,821)	(19,876)	-
Total	$ (176,175)	$ (120,154)	$ (89,581)

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

9. Income Taxes (Continued)

The Company's income tax provision (benefit) consisted of the following (in thousands):

	Years ended December 31,		
	2016	**2015**	**2014**
Current:			
Federal	$ -	$ -	$ -
State	3	(2,015)	(10,422)
Foreign	95	44	-
	98	(1,971)	(10,422)
Deferred:			
Federal	-	-	-
State	-	-	-
Foreign	-	-	-
	-	-	-
Total	$ 98	$ (1,971)	$ (10,422)

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

	Years Ended December 31,		
	2016	**2015**	**2014**
Statutory federal tax rate	34%	34%	34%
Permanent items	(3)%	(4)%	(3)%
State income taxes, net of federal benefit	4%	4%	(7)%
R&D and other tax credits	8%	12%	5%
Foreign income taxes	(4)%	(1)%	0%
Change in state tax rate	0%	0%	0%
Change in valuation allowance	(39)%	(43)%	(17)%
Other	0%	0%	0%
Effective tax rate	0%	2%	12%

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

9. Income Taxes (Continued)

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,	
	2016	2015
	(in thousands)	
Deferred tax assets:		
Net operating loss carryforwards	$ 228,729	$ 195,052
General business credits	50,648	33,360
Product license	11,783	-
Alternative minimum tax (AMT) credit	418	418
Other	16,265	10,569
Gross deferred tax assets	$ 307,843	$ 239,399
Deferred tax liabilities:		
In-process research and development	$ (23,245)	$ (23,245)
Deferred tax liabilities	$ (23,245)	$ (23,245)
Net deferred tax assets	$ 284,598	$ 216,154
Valuation allowance	(284,598)	(216,154)
Net deferred tax assets	$ -	$ -

The net deferred tax assets (prior to applying the valuation allowance) of $284.6 million and $216.2 million at December 31, 2016 and 2015, 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 $68.4 million and $52.3 million in 2016 and 2015, respectively, as it was more likely than not that such tax benefits will not be realized.

At December 31, 2016, the Company had federal net operating loss carryforwards for income tax purposes of approximately $619.0 million. Due to the limitation on NOLs as more fully discussed below, $440.7 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 $193.1 million of New Jersey NOLs available to offset against future taxable income. 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 for potential 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 were subject to substantial limitations under Section 382 due to ownership changes that occurred at

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

9. Income Taxes (Continued)

various points from the Company's original organization through December 2010. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of shareholders that own, directly or indirectly, 5% or more of a corporation's stock, 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 Other 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, to exploit such system with ARIKAYCE for the treatment of such indications, but the Company cannot manufacture such nebulizers except as permitted under the Commercialization Agreement with PARI. Under the licensing agreement, the Company paid PARI an upfront license fee and PARI is entitled to receive 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 commercial net sales of ARIKAYCE, subject to certain specified annual minimum royalties. See below for information related to the commercialization agreement with PARI.

Respironics In November 2015, the Company entered into an agreement with Respironics Inc., a division of Philips (Respironics), for the clinical supply of devices to be used in the development of INS1009 for PAH. The agreement calls for payments to Respironics upon the achievement of certain clinical milestones relating to the development of INS1009 aggregating $7.6 million. In addition, the Company will be required to pay a royalty on net sales of the product, if any.

Other 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 ARIKAYCE. If ARIKAYCE becomes an approved product for CF in the US, the

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

10. License and Other Agreements (Continued)

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 five years of the drug commercialization, the Company would owe an additional payment of $3.9 million. Since there is significant development and regulatory risk associated with ARIKAYCE, including with respect to the CF indication, the Company has not accrued these obligations.

Therapure Biopharma Inc. In February 2014, the Company entered into a Contract Manufacturing Agreement with Therapure Biopharma Inc. (Therapure) for the manufacture of ARIKAYCE. Pursuant to the agreement, the Company and Therapure collaborated to construct a production area for the manufacture of ARIKAYCE in Therapure's existing manufacturing facility in Mississauga, Ontario, Canada. Therapure manufactures 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. Under the agreement, the Company is obligated to pay certain minimum amounts for the batches of ARIKAYCE produced each calendar year. 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 LAI. The Commercialization Agreement envisages that PARI will undertake the manufacturing of the Device except in the case of certain defined supply failures, when the Company will have the right to make the Device and have it made by third parties (but not certain third parties deemed under the Commercialization Agreement to compete with PARI). The agreement has an initial term of fifteen years from the first commercial sale of ARIKAYCE pursuant to the licensing agreement (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) in limited circumstances, upon termination by the Company of the License Agreement between the parties.

SynteractHCR, Inc. In December 2014, the Company entered into a services agreement with SynteractHCR, Inc. (Synteract) pursuant to which the Company retained Synteract to perform implementation and management services in connection with the 212 study. In April 2015, the

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

10. License and Other Agreements (Continued)

Company entered into a work order with Synteract to perform implementation and management services for the 312 study.

Ajinomoto Althea, Inc. In September 2015, the Company entered into a Commercial Fill/Finish Services Agreement (the Fill/Finish Agreement) with Ajinomoto Althea, Inc., a Delaware corporation (Althea), for Althea to produce, on a non-exclusive basis, ARIKAYCE in finished dosage form. Under the Fill/Finish Agreement, the Company is obligated to pay a minimum of $2.7 million for the batches of ARIKAYCE produced by Althea each calendar year during the term of the Fill/Finish Agreement. The Fill/Finish Agreement became effective as of January 1, 2015, with an initial term that was to end on December 31, 2017. In 2016, the term was extended for an additional two years through December 31, 2019, and may be extended for additional two-year periods upon mutual written agreement of the Company and Althea at least one year prior to the expiration of its then-current term. The Company has spent more than the required minimum for batches of ARIKAYCE in each year of the contract.

AstraZeneca In October 2016, the Company entered into a license agreement (License Agreement) with AstraZeneca AB, a Swedish corporation (AstraZeneca). Pursuant to the terms of the License Agreement, AstraZeneca granted the Company exclusive global rights for the purpose of developing and commercializing AZD7986 (renamed INS 1007). In consideration of the licenses and other rights granted by AstraZeneca, the Company made an upfront payment of $30.0 million, which was included as research and development expense in the fourth quarter of 2016. The Company is also obligated to make a series of contingent milestone payments totaling up to an additional $85.0 million upon the achievement of clinical development and regulatory filing milestones. If the Company elects to develop INS1007 for a second indication, the Company will be obligated to make an additional series of contingent milestone payments totaling up to $42.5 million. No additional milestone payments are due for any indications beyond the first and second indications. In addition, the Company will pay AstraZeneca tiered royalties ranging from a high single-digit to mid-teen on net sales of any approved product based on INS1007 and one additional payment of $35.0 million upon the first achievement of $1 billion in annual net sales. The License Agreement provides AstraZeneca with the option to negotiate a future agreement with the Company for commercialization of INS1007 in chronic obstructive pulmonary disease or asthma.

11. Commitments and Contingencies

Commitments

The Company has an operating lease for office and laboratory space located in Bridgewater, NJ for which the initial lease term expires in November 2019. Future minimum rental payments under this lease are $3.0 million. In July 2016, the Company signed an operating lease for additional laboratory space located in Bridgewater, NJ for which the initial lease term expires in September 2021. Future minimum rental payments under this lease are $2.1 million.

Rent expense charged to operations was $1.2 million, $0.8 million, and $1.3 million for the years ended December 31, 2016, 2015 and 2014, respectively. Rent expense is recorded on a

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

11. Commitments and Contingencies (Continued)

straight-line basis over the term of the applicable leases. Future minimum rental cash payments required under the Company's operating leases as of December 31, 2016 are as follows (in thousands):

Year Ending in December 31:		
2017	$	1,445
2018		1,482
2019		1,388
2020		443
2021		461
	$	5,219

Legal Proceedings

On July 15, 2016, a lawsuit captioned Hoey v. Insmed Incorporated, et al, No. 3:16-cv-04323-FLW-TJB (D.N.J. July 15, 2016) was filed in the US District Court for the District of New Jersey on behalf of a putative class of investors who purchased the Company's common stock from March 18, 2013 through June 8, 2016. The complaint alleged that the Company and certain of its executives violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 (Exchange Act) by misrepresenting and/or omitting the likelihood of the EMA approving the Company's European MAA for use of ARIKAYCE in the treatment of NTM lung disease and the likelihood of commercialization of ARIKAYCE in Europe.

On October 25, 2016, the Court issued an order appointing Bucks County Employees Retirement Fund as lead plaintiff for the putative class. On December 15, 2016, lead plaintiff filed an amended complaint that shortens the putative class period for the Exchange Act claims to March 26, 2014 through June 8, 2016 and adds claims under Sections 11, 12, and 15 of the Securities Act on behalf of a putative class of investors who purchased common stock in or traceable to the Company's March 31, 2015 public offering. The amended complaint names as defendants in the Securities Act claims the Company, certain directors and officers, and the investment banks who served as underwriters in connection with the secondary offering. The amended complaint alleges defendants violated the Securities Act by using a purportedly misleading definition of "culture conversion" and supposedly failing to disclose in the offering materials purported flaws in the Phase 2 study that made the secondary offering risky or speculative. The amended complaint seeks damages in an unspecified amount. The Company's response to the amended complaint, which it intends to move to dismiss, is due by March 1, 2017. The Company believes that the allegations in the complaints are without merit and intends to defend the lawsuit vigorously; however, there can be no assurance regarding the ultimate outcome of the lawsuit.

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.

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INSMED INCORPORATED

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

12. Quarterly Financial Data (Unaudited)

The following table summarizes unaudited quarterly financial data for the years ended December 31, 2016 and 2015 (in thousands, except per share data).

	2016				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter*	Total*
Revenues	$ -	$ -	$ -	$ -	$ -
Operating loss	$ (33,067)	$ (36,133)	$ (37,149)	$ (67,051)	$ (173,400)
Net loss	$ (33,532)	$ (36,579)	$ (37,760)	$ (68,402)	$ (176,273)
Basic and diluted net loss per share	$ (0.54)	$ (0.59)	$ (0.61)	$ (1.10)	$ (2.85)

	2015				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
Revenues	$ -	$ -	$ -	$ -	$ -
Operating loss	$ (26,706)	$ (27,952)	$ (30,245)	$ (32,590)	$ (117,493)
Net loss	$ (27,369)	$ (28,607)	$ (30,962)	$ (31,245)	$ (118,183)
Basic and diluted net loss per share	$ (0.55)	$ (0.47)	$ (0.50)	$ (0.51)	$ (2.02)

* Includes a $30.0 million upfront payment to AstraZeneca under the AZ License Agreement related to INS1007, which was included as a component of research and development expense.

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 US employees and permits voluntary contributions by employees subject to IRS-imposed limitations. Beginning in April 2015, the Company matched 100% of eligible employee contributions on the first 3% of employee salary (up to the IRS maximum). Employer contributions for the year ended December 31, 2016 and 2015 were $0.6 and $0.4 million, respectively.

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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 (SEC file no. 000-30739)).
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 filed on March 18, 2013).
3.2	Amended and Restated Bylaws of Insmed Incorporated (incorporated by reference from Exhibit 3.1 to Insmed Incorporated's Quarterly Report on Form 10-Q filed on August 6, 2015).
4.1	Specimen stock certificate representing common stock, $0.01 par value per share, of the Registrant (incorporated by reference from Exhibit 4.2 to Insmed Incorporated's Registration Statement on Form S-4/A (Registration No. 333-30098) filed on March 24, 2000).
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**	Insmed Incorporated 2015 Incentive Plan (incorporated by reference from Exhibit 99.1 to Insmed Incorporated's Registration Statement on Form S-8 filed on May 28, 2015).
10.4**	Form of Award Agreement for Restricted Stock Units issued to employees pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.3 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.5**	Form of Award Agreement for Restricted Stock Units issued to directors pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.4 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.6**	Form of Award Agreement for an Incentive Stock Option pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.5 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.7**	Form of Award Agreement for a Non-Qualified Stock Option pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.6 to Insmed Incorporated's Form 10-K filed on March 6, 2014).
10.8**	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).

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10.9**	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).
10.10	Amended and Restated Loan and Security Agreement, dated as of September 30, 2016, by and between Insmed Incorporated, Celtrix Pharmaceuticals, the subsidiaries joined thereto, the lenders party thereto and Hercules Capital, Inc., as agent (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Quarterly Report on Form 10-Q filed on November 3, 2016).
10.11	Settlement, license and development agreement, dated March 5, 2007, between Insmed Incorporated, Insmed Therapeutic Proteins, Inc., Celtrix Pharmaceuticals, Tercica Inc., and Genentech, Inc. (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Quarterly Report on 10-Q filed on May 10, 2007 (SEC file no. 000-30739)).
10.12	License agreement, dated April 25, 2008, between Transave, Inc. and PARI Pharma GmbH, and Amendments No. 1-4 thereto (incorporated by reference from Exhibit 10.22 to Insmed Incorporated's Annual Report on Form 10-K filed on March 18, 2013).
10.12.1	Amendment No. 5 to License Agreement between Transave, Inc. and PARI Pharma GmbH, effective as of October 5, 2015 (incorporated by reference from Exhibit 10.14.1 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.12.2	Amendment No. 6 to License Agreement between Transave, Inc. and PARI Pharma GmbH, effective as of October 9, 2015 (incorporated by reference from Exhibit 10.14.2 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.13**	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).
10.14**	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).
10.15	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).
10.15.1	First Amendment to Lease, dated April 29, 2014, between Denver Road, LLC and Insmed Incorporated (incorporated by reference from Exhibit 10.17.1 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.15.2	Second Amendment to Lease, dated November 20, 2015, between Denver Road, LLC and Insmed Incorporated (incorporated by reference from Exhibit 10.17.2 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.16	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).

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10.17	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).
10.18	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).
10.19	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).
10.20	Stock Purchase Agreement, dated as of December 15, 2014, by and between Insmed Incorporated and Hercules Technology Growth Capital, Inc. (incorporated by reference from Exhibit 10.28 to Insmed Incorporated's Form 10-K filed on February 27, 2015).
10.21	Master Agreement for Services, dated as of August 27, 2014, by and between Insmed Incorporated and SynteractHCR, Inc. (incorporated by reference from Exhibit 10.29 to Insmed Incorporated's Form 10-K filed on February 27, 2015).
10.22	Work Order 1, dated as of December 30, 2014, by and between Insmed Incorporated and SynteractHCR, Inc. (incorporated by reference from Exhibit 10.30 to Insmed Incorporated's Form 10-K filed on February 27, 2015).
10.23	Change in Scope 1 to Work Order 1, dated as of May 27, 2016, by and between Insmed Incorporated and SynteractHCR, Inc. (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed August 4, 2016).
10.24**	Employment Agreement, effective as of February 18, 2014, between Insmed Incorporated and Peggy Berry (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on May 7, 2015).
10.25**	Employment Agreement, effective as of January 2, 2013, between Insmed Incorporated and S. Nicole Schaeffer (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on May 7, 2015).
10.26	Commercial Fill/Finish Services Agreement between Insmed Incorporated and Ajinomoto Althea, Inc., dated as of September 15, 2015 (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed November 6, 2015).
10.27	Lease Agreement, effective as of July 1, 2016, by and between Insmed Incorporated and CIP II/AR Bridgewater Holdings, LLC (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed August 4, 2016).
10.28**	Employment Agreement, effective as of September 27, 2016, between Insmed Incorporated and Roger Adsett (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed November 3, 2016).
10.29*	License Agreement, dated October 4, 2016, between Insmed Incorporated and AstraZeneca AB (filed herewith).

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10.30	Extension of Commercial Fill/Finish Services Agreement between Insmed Incorporated and Ajinomoto Althea, Inc., dated as of November 30, 2016 (filed herewith).
10.31	Amendment to Employment Agreement, effective as of September 26, 2016, between Insmed Incorporated and Christine Pellizzari (filed herewith).
10.32	Amendment to Employment Agreement, effective as of September 26, 2016, between Insmed Incorporated and S. Nicole Schaeffer (filed herewith).
21.1	Subsidiaries of Insmed Incorporated (filed herewith).
23.1	Consent of Ernst & Young LLP (filed herewith).
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 (filed herewith).
31.2	Certification of William H. Lewis, Chief Executive Officer of Insmed Incorporated, pursuant to 18 USC Section 1350, as adopted pursuant to Section 906 of the Sarbanes Oxley Act of 2003 (filed herewith).
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 (filed herewith).
32.2	Certification of Andrew T. Drechsler, Chief Financial Officer (Principal Financial and Accounting Officer) of Insmed Incorporated, pursuant to 18 USC Section 1350, as adopted pursuant to Section 906 of the Sarbanes Oxley Act of 2003 (filed herewith).
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

*
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.

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