INSMED INC
Form 10-K
March 06, 2014

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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, 2013

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.)**
9 Deer Park Drive, Suite C Monmouth Junction, NJ 08852	**(732) 997-4600**
(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 [ ] No [ü]

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 [ ] Accelerated filer [ü] 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, 2013, was $345.2 million (based on the closing price for shares of the registrant's Common Stock as reported on the Nasdaq Capital Market on that date). In determining this figure, the registrant has assumed solely for this purpose that all of its directors, executive officers, persons beneficially owning 10% or more of the outstanding Common Stock and certain other stockholders of the registrant may be considered to be affiliates. This assumption shall not be deemed conclusive as to affiliate status for this or any other purpose.

On February 27, 2014, there were 39,263,837 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 2014 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission no later than 120 days, or April 30, 2014, after the registrant's fiscal year ended December 31, 2013, and to be delivered to shareholders in connection with the 2014 Annual Meeting of Shareholders, are herein incorporated by reference in Part III of this Form 10-K.

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

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

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

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

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PART I

ITEM 1. BUSINESS

BUSINESS OVERVIEW

Insmed is a biopharmaceutical company focused on developing and commercializing inhaled therapies for patients battling serious lung diseases that are often life threatening. Our lead product candidate, ARIKAYCE®, or liposomal amikacin for inhalation (LAI), is an inhaled antibiotic treatment that delivers a proven and potent anti-infective directly to the site of serious lung infections.

We are currently conducting a phase 2 clinical trial in the United States (US) and Canada of ARIKAYCE in patients who have lung infections caused by non-tuberculous mycobacteria (NTM) and we expect to report top-line clinical results from the double-blind phase of this clinical trial in March 2014. In 2013, we concluded a phase 3 clinical trial in Europe and Canada of ARIKAYCE in cystic fibrosis (CF) patients who have lung infections caused by *Pseudomonas aeruginosa* (*Pseudomonas*). The CF and NTM target indications address orphan patient populations. Our strategy includes plans to continue to develop ARIKAYCE to broaden the NTM indication and for additional indications beyond *Pseudomonas* in CF and NTM. We also plan to develop, acquire, in-license or co-promote other products that address orphan or rare diseases in the fields of pulmonology and infectious disease. Our current primary development focus is to obtain regulatory approval for ARIKAYCE in these two initial indications and to prepare for commercialization in the United States, Europe, Canada and Japan. We anticipate that if approved, ARIKAYCE would be the first once-a-day inhaled antibiotic treatment option available for these CF and NTM indications. The following table summarizes the current status of ARIKAYCE development.

Product Candidate/Target Indications	Status	Next Expected Milestones
ARIKAYCE Non-tuberculous mycobacteria (NTM) lung infections	Completed enrollment of 90 patients in our phase 2 clinical trial in the United States and Canada.	We expect to report top-line clinical results from our phase 2 clinical trial in March 2014.
	Granted orphan drug designation in Europe and the United States.	We expect to enroll the first patient in our single-arm, open label, supportive study in the United States and Europe during the second quarter of 2014.
	Granted Qualified Infectious Disease Product ("QIDP") designation, which includes Priority Review, by the U.S. Food and Drug Administration ("FDA") in June 2013.	We expect to have dialogue with the FDA and the European Medicines Agency ("EMA") in the second quarter of 2014 to discuss the regulatory pathway.
	Granted Fast Track designation by the FDA in June 2013 which permits a rolling submission of	

a New Drug Application ("NDA").	If approved, we expect ARIKAYCE would be the first approved inhaled antibiotic treatment for NTM lung infections.
	We are developing plans to commercialize ARIKAYCE, if approved, initially in the United States, in certain countries in Europe, and Canada and eventually Japan.

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Product Candidate/Target Indications	Status	Next Expected Milestones
ARIKAYCE *Pseudomonas aeruginosa* lung infections in CF patients	Reported top-line results from our phase 3 clinical trial for registration in Europe and Canada in July 2013, in which once-daily ARIKAYCE achieved its primary endpoint of non-inferiority when compared to twice-daily tobramycin inhaled solution.	We expect to submit regulatory filings with the EMA and Health Canada in the middle of 2014. If the EMA allows a filing that includes both the CF and NTM indication we will most likely submit our filing in the second half of 2014.
	Conducting a two-year, open-label safety study in patients that completed our phase 3 clinical trial in Europe and Canada. We expect to complete this study in mid-2015.	We expect to evaluate our plans for this indication in the United States after reviewing the results from our phase 2 clinical trial in NTM.
	Reported top-line results from the first group of patients that completed the first year of the two-year open label extension study.	We are developing plans to commercialize ARIKAYCE, if approved, in certain countries in Europe and in Canada where we expect it would be the only once-a-day treatment for Pa lung infections in CF patients.
	Granted orphan drug designation in Europe and the United States.	
ARIKAYCE *Pseudomonas aeruginosa* and other susceptible organisms causing lung infections in non-CF bronchiectasis patients	Completed phase 2 study in the United States.	We expect to evaluate development and commercialization strategies for this indication when we complete our phase 2 clinical trial in patients with NTM infections.
	Granted orphan drug designation in the United States.	

For FDA marketing application and review purposes ARIKAYCE is considered a new molecular entity (NME) primarily due to its proprietary liposomal technology. For a description of our liposomal technology, see " Our Proprietary Liposomal Technology." The FDA has indicated that it considers ARIKAYCE a NME for application and review purposes even though the agency has previously approved drugs with the active ingredient, amikacin sulfate. FDA characterizes some drugs as NMEs for administrative purposes, even if they contain an active moiety (the molecule or ion responsible for the action of the drug substance) that is closely related to active moieties in products that have previously been approved by FDA. Amikacin sulfate is an FDA-approved antibiotic with proven efficacy in the treatment of a broad range of gram-negative infections, including Pseudomonas and NTM. ARIKAYCE is in the aminoglycoside class of antibiotics.

If approved for NTM patients, we expect ARIKAYCE would be the first and only approved inhaled antibiotic for the treatment of NTM lung infections. If approved for CF patients with Pseudomonas lung infections, we expect ARIKAYCE would be the first inhaled antibiotic to be

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approved for once-daily administration in this indication. ARIKAYCE has been granted the following orphan drug designations (the significance of that status is described further in the *Government Regulation* section):

US: NTM lung infections, *Pseudomonas* lung infections in CF patients, and lung infections in non-CF bronchiectasis patients; and

European Union (EU): NTM lung infections and *Pseudomonas* lung infections in CF patients.

Corporate History

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

Our Strategy

Our strategy is to focus on the development and commercialization of innovative inhaled therapies for patients with serious lung diseases in orphan indications. While we believe that ARIKAYCE has the potential to treat many different diseases, our attention is initially focused on regulatory approval and commercialization preparation for our two initial indications: (1) NTM lung infections and (2) *Pseudomonas* lung infections in CF patients. Our current priorities are as follows.

Continue generating additional clinical data from studies showing the effects of ARIKAYCE to treat NTM lung infections and *Pseudomonas* lung infections in CF patients necessary for new drug applications in Europe, Canada, Japan and the United States;

Actively pursue new drug filings to secure approval for ARIKAYCE to treat NTM lung infections in the United States, Europe, Canada and Japan;

Actively pursue new drug filings to secure approval for ARIKAYCE to treat *Pseudomonas* lung infections in CF patients in Europe and Canada;

Expand our product supply chain in support of clinical development and if approved, commercialization;

Prepare for commercial launch in the NTM indication in the United States, Europe, Canada and eventually Japan and certain other countries including Korea, Taiwan and China;

Prepare for commercial launch in *Pseudomonas* in CF patients indication in Europe and Canada;

Attempt to develop, acquire, in-license or co-promote promising late stage or commercial products that we believe are complementary to ARIKAYCE and our core competencies; and

Continue to develop novel formulations of existing therapies, where such reformulation could materially improve the treatment paradigm for the underlying disease or to enable pursuit of a new indication.

In support of these priorities, we completed our registrational phase 3 clinical study of ARIKAYCE in CF patients with *Pseudomonas* lung infections in Europe and Canada. We plan to complete our regulatory filings in Europe and Canada for this indication in the middle of 2014. If the EMA allows a filing that includes both the CF and NTM indication we will most likely submit our filing in the second half of 2014. We completed enrollment in our US and Canadian phase 2 clinical study of ARIKAYCE in patients with recalcitrant NTM lung infections. We intend to launch a single-arm, open label, supportive study in the US and Europe during the second quarter of 2014 for other patients with NTM lung infections who cannot tolerate existing therapy as determined by their prescribing physician. We plan to scale up manufacturing, we are identifying second source suppliers, and we plan to implement supply and quality agreements in preparation for commercialization of ARIKAYCE. We also intend to continue to work closely with PARI Pharma GmbH (PARI), the

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manufacturer of our drug delivery nebulizer, to address our commercial supply needs. We have commenced the build-out of our commercial infrastructure in preparation for potential commercial launches in Europe, Canada and the US. We will continue to evaluate opportunities for additional products through various business development channels.

Product Candidates

Our lead product candidate, ARIKAYCE, or LAI, is a once-a-day inhaled antibiotic treatment engineered to deliver an anti-infective directly to the site of serious lung infections. There are two key components of ARIKAYCE: the liposomal formulation of the drug and the nebulizer device through which ARIKAYCE is inhaled via the mouth and into the lung. The nebulizer technology is owned by PARI, but we have exclusive access to this technology, which is specifically developed for the delivery of our liposomal encapsulation of amikacin, through our licensing agreement with PARI. Our proprietary liposomal technology and nebulizer are designed specifically for delivery of pharmaceuticals to the lung and provides for potential improvements to existing treatments. We believe that ARIKAYCE has potential usage for at least two orphan patient populations with high unmet need: patients who have NTM lung infections and CF patients who have *Pseudomonas* lung infections. We estimate the combined global market potential for these two orphan indications to be approximately $1 billion.

ARIKAYCE has the potential to be differentiated from amikacin and certain marketed drugs for the treatment of chronic lung infections if it can be demonstrated to provide improved efficacy, safety and patient convenience. We believe ARIKAYCE's ability to deliver high, sustained levels of amikacin directly to the lung and to the specific site of the underlying infection could distinguish it from other alternatives. We are also investigating ARIKAYCE's potential for durability of effect, benefiting patients when off treatment or for an extended period of treatment. In addition, the inhalation delivery of ARIKAYCE may reduce the potential for adverse events such as ototoxicity (hearing loss, ringing in the ears and/or loss of balance) and nephrotoxicity (toxicity to the kidneys), as compared with intravenous (IV) administration of amikacin. If approved, we expect that ARIKAYCE will be administered once-daily for approximately 13 minutes via inhalation using the eFlow® Nebulizer System, which has been optimized specifically for ARIKAYCE by PARI. We believe that this nebulizer system will reduce treatment time or dosing frequency, as compared with the currently marketed inhaled antibiotics, which require dosing two to three times daily with treatment times ranging from approximately 10 to 40 minutes per day. By easing the patient's treatment burden we believe that ARIKAYCE can potentially improve patient compliance, which we believe may in turn lead to a reduction in the development of antibiotic resistance and, ultimately, lead to clinical benefit.

We believe that ARIKAYCE may provide: (1) improved efficacy resulting from sustained deposition of drug in the lung and improved ability to reach the site of infection (for CF *Pseudomonas* infections, this means penetration of biofilm and facilitated drug release by factors that are secreted by the bacteria, and for NTM, this means enhanced uptake into macrophages, where NTM often grows); (2) decreased adverse events and improved tolerability as compared with amikacin delivered intravenously; and (3) reduced dosing frequency or treatment time as compared to existing products. In the future we may conduct head-to-head comparative studies that would be necessary to make comparative statements against other products.

ARIKAYCE for Patients with NTM Lung Infections

Overview of NTM Lung Infections

Non-tuberculous *mycobacteria,* or NTM, are organisms common in soil and water that have been associated with lung disease in select patient groups. NTM have characteristics that are similar to tuberculosis, or TB, but NTM are not contagious. Many people have NTM in their bodies, but NTM do not normally lead to an infection, perhaps because the body's immune system successfully overcomes the threat of infection. It is not completely understood why certain individuals are

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susceptible to NTM infections. However, the patients who become infected by NTM often are immune-compromised, due to comorbidities such as HIV or rheumatoid arthritis, or have structural damage in their lungs, due to smoking, chronic obstructive pulmonary disease ("COPD") or CF, at the time of the infection.

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

Current Treatment Options and Limitations

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

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

Market

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

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

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

ARIKAYCE for NTM Lung Infections: Potential Advantages and Distinguishing Features

If approved, ARIKAYCE would be the first and only approved treatment for patients battling NTM lung infections.

Liposomal Design and Formulation

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

Preclinical Activity

ARIKAYCE has been shown to have superior *in vitro* activity against MAC and *M. abscessus* when compared with amikacin solution (study conducted by L.E. Bermudez at Oregon State University, data on file, 2010). ARIKAYCE also has been shown to more effectively kill certain forms of NTM in cultured lung phagocytes as compared to soluble amikacin.

Route of Administration

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

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Anticipated Dosage Regimen

We believe ARIKAYCE, if approved, could improve patient convenience by providing once-a-day dosing. According to *SDI Healthcare Database* NTM patients average 7.6 antibiotic courses and 10.2 hospital days per year. We anticipate that ARIKAYCE will be administered once daily outside of the hospital for approximately 13 minutes per day for a period of 84 days for this indication. We believe that an effective inhaled treatment that improves the outcomes for an NTM patient would represent a significant benefit in the patient's quality of life.

Current Clinical Program

We are currently conducting a phase 2 clinical trial in the US and Canada for ARIKAYCE in adult patients with recalcitrant NTM lung infections. We completed enrollment in October 2013 and last patient last visit occurred in January 2014. The phase 2 clinical trial is a randomized, placebo-controlled study of 90 adult patients with recalcitrant NTM lung infections. There are two parts to the study: a randomized portion and an open-label portion. Additionally, we have initiated a scintigraphy sub-study to examine drug deposition and distribution of ARIKAYCE in the lung.

In the randomized portion of the study, patients were screened to include in the study those who have NTM lung infections with persistent sputum culture positive for MAC or *M. abscessus* while on ATS/IDSA-guidelines-based treatment regimen for at least six months prior to screening. Patients who are NTM culture positive and meet the eligibility criteria to enroll in the study received, in addition to their ongoing antibiotic treatment regimen, either ARIKAYCE 590 mg or a placebo both delivered once daily via an optimized, investigational eFlow Nebulizer System.

The primary efficacy endpoint for this study is the change in mycobacterial density from baseline to the end of 84 days of treatment. There is a pre-specified stratification of patients with MAC versus M. *abscessus* and patients with and without cystic fibrosis. The study will also measure certain secondary, tertiary and exploratory endpoints, including but not limited to: the proportion of patients with culture conversion to negative, the time to "rescue" anti-mycobacterial drugs, the change from baseline in six-minute walk distance and oxygen saturation, the change from baseline in patient reported outcomes, and evaluation of safety and tolerability. At the conclusion of the randomized portion of the study, eligible patients will receive ARIKAYCE once daily for an additional 84 days during the open-label portion of the study, primarily to measure longer-term safety and efficacy. We previously agreed with the FDA on this clinical trial design. We expect results from the randomized portion of the clinical trial in March 2014.

In addition to the phase 2 clinical trial outlined above, we will launch a single-arm, open label, supportive study with planned sites in the US, Europe, Australia and Canada. We currently anticipate this program's participants will consist of approximately 50 patients who have NTM lung infection but are not eligible for entry into our phase 2 clinical trial. We believe that clinical data collected from the experience with these patients may help regulatory authorities to evaluate ARIKAYCE's safety and suitability for treating NTM lung infection patients.

ARIKAYCE received orphan drug status in the US and Europe for the treatment of NTM.

Development History

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

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

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

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

Strategy for Commercialization

We currently plan to retain marketing rights for ARIKAYCE for NTM indications globally. Given the current lack of approved treatments for NTM lung infections, we believe we will immediately have a strong market position if ARIKAYCE is approved for commercialization in the NTM indication. We believe ARIKAYCE will require a limited commercial infrastructure because of the small focused nature of the potential physician prescribing population for NTM patients. In 2013, we commenced preparations for the potential commercialization of ARIKAYCE, including hiring Matt Pauls, our Chief Commercial Officer. We plan to fill several other new positions to support our future sales and marketing efforts. We may also seek to out-license ARIKAYCE outside of Europe, Canada and the US.

ARIKAYCE for CF Patients with *Pseudomonas* Lung Infections

Overview of CF and Pseudomonas Lung Infections

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

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Despite extensive treatment with multiple antibiotics, improved nutrition, and other treatments, life expectancy of a CF patient is only about 37 years (Cystic Fibrosis Foundation Patient Registry, 2011). Median predicted age of survival is calculated using life table analysis (as calculated by actuaries) given the ages of the patients in the registry and the distribution of deaths. Using this calculation, half of the people in the patient registry are expected to live beyond the median predicted survival age, and half are expected to live less than the median predicted survival age.

Among other issues, CF causes thick, sticky mucus to develop in and clog the lungs. This creates an ideal environment for various pathogens, such as *Pseudomonas*, to colonize and lead to chronic infection of the lung, inflammation and progressive loss of lung function. In fact, chronic bronchial infections with *Pseudomonas* are a major cause of morbidity and mortality among patients with CF. Once a CF patient acquires a *Pseudomonas* infection, it is difficult to eradicate. The current, best available treatment is chronic administration of antibiotics to suppress the bacteria, reduce inflammation and preserve lung function for as long as possible. The rate of infection with *Pseudomonas* in CF patients increases with age. It is estimated that 70% of adult CF patients have chronic infection due to *Pseudomonas* (CFF Patient Registry, 2011). A study reported in the *Journal of Cystic Fibrosis* (Liou, 2010) found that deterioration in lung function of CF patients is the main cause of death and that, despite best efforts, lung function declines by 1% to 3% annually.

Current Treatment Options and Limitations

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

Antibiotics delivered via inhalation are part of the standard treatment for CF patients with *Pseudomonas* lung infections and are generally thought to be a way to deliver more active drug directly to the site of infection compared with other routes of administration. The most used treatment in the US for the management of chronic *Pseudomonas* infection in subjects with CF is suppressive therapy with tobramycin. One example is twice daily Tobi inhaled solution, which is approved by the FDA for CF patients ages six years and above with a FEV1 (forced expiratory volume in 1 second) of 25%-75%, has been sold in the US since January 1998. A 1999 study reported that Tobi, 300 mg, administered twice a day for cycles of 28 days followed by 28-days-off treatment was shown to reduce *Pseudomonas* colony counts, increase FEV1 percent predicted, reduce hospitalizations and decrease additional antibiotic use (Ramsey et al., 1999, New England Journal of Medicine). High levels of tobramycin can be attained in the lung with relatively low systemic exposure with inhaled drug compared to intravenous tobramycin. However, patients using Tobi must be dosed twice a day for approximately 15 to 20 minutes of inhalation session per dose for a total of approximately 30 to 40 minutes per day. Recent data show that the effect of Tobi on pulmonary function in CF patients has lessened since its introduction into the marketplace more than a decade ago (Konstan et al., Journal of Cystic Fibrosis, January 2011, and Assael et al., 34th European Cystic Fibrosis Society Conference, Poster 86, June 2011). In addition, according to information presented at a FDA advisory panel, resistance to Tobi has increased 85% in the ten-year period from 1999 to 2009 (FDA advisory panel US-FDA-AIDAC for Tobi-Podhaler, September 2012).

Market

We estimate that the global market for the treatment of *Pseudomonas* lung infections in CF patients is approximately $500 million. We believe this market is being driven by physicians' desire to

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maintain the lung function of CF patients, which continues to decline in many patients despite extensive treatment with current therapies including currently approved inhaled antibiotics. We believe that the following additional factors may lead to further market growth:

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

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

Patient Compliance Considerations

We believe ARIKAYCE may facilitate better patient compliance with prescribed treatment regimens; patient compliance with or "adherence" to prescribed treatment is generally expected to impact the effectiveness of treatment. If a product can improve adherence, it may be able to differentiate itself from other marketed drugs. In the case of treatment and management of chronic *Pseudomonas* lung infections in CF patients, currently the most used treatment in the US is suppressive therapy with 300 mg twice daily of Tobi inhaled solution and tobramycin inhaled powder. Tobi is administered twice daily for 28 days followed by a 28-day-off period. This cycle of "on and off" treatment is repeated in a chronic pattern. We anticipate that ARIKAYCE would be administered once daily for approximately 13 minutes per day for 28 days followed by a 28-day off-drug period. We believe that any inhaled treatment that reduces the treatment burden on a CF patient could represent a significant improvement in the patient's quality of life and result in improved compliance, as well as reduce the development of antibiotic resistance.

Liposomal Design and Formulation

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

In addition, ARIKAYCE has demonstrated a prolonged half-life in animals' lungs. We believe this effect is due to our proprietary liposomal technology. One important measure of the effectiveness

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of antibiotics is the maintenance of anti-bacterial drug levels in the lung above the minimum inhibitory concentration. We anticipate that ARIKAYCE will be maintained in the human lung in a manner similar to what was demonstrated in animal studies.

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

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

Route of Administration

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

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

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

Limited Penetration. There is limited penetration into and through the sputum/biofilm matrix by aminoglycoside antibiotics. The antibiotics are positively charged and the biofilm is negatively charged. As a result the antibiotics bind to the biofilm and the availability of the drug at the location of the microorganism is suboptimal. We believe that our proprietary liposomal technology will result in localized targeting of drugs, leading to increased availability

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of the drug at the location of the microorganism, while significantly reducing drug exposure at non-disease sites throughout the body and reducing the occurrence of systemic drug-related toxicity.

Current Clinical Program

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

ARIKAYCE achieved its primary endpoint of non-inferiority to Tobi for relative change in FEV_1 from baseline to the end of the study;

Overall, secondary endpoints, as summarized above, showed comparability of once-daily ARIKAYCE compared with twice-daily Tobi; and

The safety profile of ARIKAYCE was comparable to Tobi during all three treatment cycles, with adverse events consistent with those seen in similar studies and expected in a population of CF patients receiving inhaled antibiotics. There was no difference between arms in the reporting of serious adverse events and there were no unexpected adverse events.

We are conducting a two-year, open label safety study in patients that also completed our registrational phase 3 clinical study of ARIKAYCE for CF patients with *Pseudomonas* lung infections in Europe and Canada. Approximately 75% of the eligible patients that completed our registrational phase 3 clinical study consented to participate in the safety study. The patients in this study will receive ARIKAYCE for up to a two year period, using the same cycles of a 28 day on-treatment period and a 28 day off-treatment period. In February 2014, we reported interim data from our two-year open label extension study which showed a mean increase in relative change in FEV_1 which was sustained during both on-treatment and off-treatment months. We expect to use this interim data from this study as part of our regulatory filings with the EMA and Health Canada, which we expect to submit during 2014, and we expect to complete this study in mid-2015.

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

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Development History

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

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

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

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

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

In connection with the FDA's decision to lift the clinical hold for the CF *Pseudomonas aeruginosa* lung infection indication, we agreed to conduct a 9 month dog inhalation toxicity study of ARIKAYCE. In 2013, we concluded the 9 month the dog inhalation toxicity study. In summary, the final report from the study stated that the lung macrophage response in dogs was similar to that seen

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in our previous 3 month dosing dog study, and there was no evidence of neoplasia, squamous metaplasia or proliferative changes.

We expect to reevaluate our plans regarding a US phase 3 clinical trial in CF patients with *Pseudomonas* lung infection after we receive the results from the ongoing phase 2 clinical trial in NTM patients in the US.

Strategy for Commercialization

We currently plan to retain marketing rights for ARIKAYCE for CF patients with *Pseudomonas* lung infections in certain countries in Europe, and in Canada and the US. We believe ARIKAYCE will require a limited commercial infrastructure in these regions because of the small focused nature of the potential physician prescribing population for CF patients. We may seek to out-license ARIKAYCE in certain countries in Europe, as well as outside of Europe, Canada and the US.

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

Disease

We believe ARIKAYCE has the potential to be used to treat non-CF bronchiectasis characterized by *Pseudomonas* lung infections. However, we are currently concentrating our development efforts on the treatment of *Pseudomonas* lung infections in CF patients and patients with NTM lung infections. We will evaluate our development and commercialization strategies for this indication when we complete our phase 2 study in patients with NTM infections.

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

Market

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

Development Program

ARIKAYCE was granted orphan drug status in the US for the treatment of bronchiectasis in patients with *Pseudomonas* or other susceptible pathogens.

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

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

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

Although we believe there is an opportunity to develop ARIKAYCE for non-CF bronchiectasis, we do not intend to initiate further clinical studies with respect to a non-CF bronchiectasis indication until we have completed additional clinical studies for CF patients with *Pseudomonas* lung infections and for patients with NTM lung infections. Following those studies, we will evaluate whether to develop ARIKAYCE further for non-CF bronchiectasis.

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

Our Proprietary Liposomal Technology

We have designed our liposomal technology specifically for use in delivering pharmaceuticals to the lung. Drugs deposited in the lung typically have short residence times, from minutes to a few hours, which is problematic for treating lung conditions where maintaining high concentrations locally in the lung for long periods of time is required. We believe our technology provides for potential improvements over the conventional inhalation method for delivering pharmaceuticals to the pulmonary system. These potential advantages include improvements in efficacy, safety and patient convenience.

Liposomes are microscopic membrane shells that contain water. Liposomes usually have a single membrane but can also be designed to have several membrane layers. These layers can be arranged like the layers of an onion or like bubbles inside of larger bubbles. In all cases, there is water in the liposome's core and between each layer. In a liposome drug delivery system, the drug is contained in the liposome and the liposomes are administered to the patient during treatment. Water soluble drugs are located in the liposome's water core, and drugs that do not dissolve in water are located in or associated with the membrane layers.

For ARIKAYCE

Nebulized ARIKAYCE is comprised of both amikacin in solution for immediate availability and amikacin inside liposomes for a sustained benefit. These liposomes are efficient delivery vehicles, and we designed ARIKAYCE liposomes for inhalation therapy. ARIKAYCE liposomes are less than 0.3 microns in mean diameter and contain amikacin in the water interior in a very high concentration. The relatively small size of the liposomes aids its ability to penetrate both patient mucus and bacterial biofilm to deliver drug close to bacteria. Our liposomes are highly compatible with lung tissue because they are formed using neutral lipids identical to those found naturally in the lung. The liposomes

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maintain drug in the lung and thus provide sustained delivery to the lung, which may be important in treating certain bacterial infections that have a significant pulmonary component.

Charge-Neutral Liposomes

We believe neutrally charged liposomes may enable greater penetration into the mucus and biofilm, thereby providing higher drug concentrations to kill bacteria which produce the biofilm. The materials found in a patient's mucus have negative charges, and biofilms that are produced by bacteria to protect themselves also have negative charges. Because opposite charges attract each other, positively charged antibiotics, like amikacin, bind to the negatively charged compounds on the surfaces of the mucus and biofilm. This binding prevents effective penetration of positively charged antibiotic drugs into the spaces in which the bacteria are located. Specifically, in the case of *Pseudomonas* lung infections in CF patients, these barriers are the patient's own sticky mucus and bacteria's protective biofilm. In the case of NTM, the barrier to effective treatment is in gaining access to the interior of infected macrophages. ARIKAYCE liposomes are effective delivery systems that penetrate these barriers and provide high levels of drug in the lung for a long time.

Potential for Increased Efficacy and with Low Drug Toxicity

A potential benefit of our inhalation drug delivery technology over systemic delivery of the same drug may be enhanced efficacy as a result of greater amounts of the drug being delivered directly to the site of disease. With higher localized antibiotic concentrations bacterial infections are more readily treated. Another advantage of localized targeting of drugs using this unique delivery system is that non-disease sites throughout the body are exposed to significantly less drug. We believe this reduces the potential for the occurrence of drug-related toxicity.

High-Efficiency Drug Encapsulation

We have designed our liposomes to encapsulate very high concentrations of drug into relatively small liposome structures. According to pre-clinical models, this efficiency allows our compact, drug-laden liposomes to physically penetrate bacteria-generated biofilms. Further, we have found that drug is released from the liposomes by disruptive factors secreted by *Pseudomonas*, which we believe will cause liposomes to release their drug contents near to where the bacteria reside in the lungs.

Endogenous Lipid Excipients

We believe the ability to release drug contents in proximity to the bacteria may reduce the chance of systemic adverse reactions. The lipid components of our compounds are the same as those found naturally in the lung, which may ensure a more natural metabolism and clearance than other drug delivery systems such as particles comprised of man-made polymers containing drug.

Our liposomal formulation is key to both the retention of amikacin in the lung, which allows once-a-day dosing, and the ability of ARIKAYCE to gain close access to bacteria either within a biofilm, as in the case in CF patients, or within infected macrophages, as in the case of NTM patients. It is localization near the bacteria that may improve efficacy by allowing high concentrations of drug to be delivered where it is needed most.

With a neutral surface charge and small size, ARIKAYCE liposomes are able to effectively penetrate the thick CF mucus and the bacteria's protective biofilm, both of which we believe restrict the availability of unencapsulated aminoglycosides such as tobramycin and amikacin. ARIKAYCE liposomes are also readily taken up by immune cells in the lung (alveolar macrophages) that "eat"

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inhaled particles. When NTM infect these immune cells, the bacteria are usually sheltered against attack from external antibiotics, but with ARIKAYCE, the uptake of the liposomes allows the drug to get inside these cells to attack the organisms.

For Other APIs

We believe that our liposomal technology can be used for the successful delivery of other low molecular weight products as well as high molecular weight compounds such as peptides, proteins and genes. Our unique lipid-based delivery systems are not dependent on the inhalation device and can be designed to be administered either as a nebulized aerosol spray or as a dry powder.

Optimized eFlow Nebulizer System

If approved for commercialization, we expect that ARIKAYCE will be administered once daily via inhalation using an eFlow Nebulizer System, optimized specifically for ARIKAYCE by PARI, a third-party vendor. For additional information about PARI and our contractual relationship with PARI, see " Manufacturing" and " License and Collaboration Agreements."

The optimized eFlow Nebulizer System is a medical device that uses PARI's patented eFlow technology to enable highly efficient delivery of inhaled medication, also called aerosolization, including liposomal formulations via a vibrating, perforated membrane that includes thousands of specially designed laser-drilled holes, which aids the delivery of ARIKAYCE to the lung. We believe the optimized eFlow Nebulizer System is state of the art and highly efficient. The eFlow Nebulizer System delivers a very high density of active drug, in a precisely defined and controlled droplet size, with a high proportion of respirable droplets delivered in a relatively short period of time. In addition, the eFlow Nebulizer System has a quiet mode of operation, is small in size, light weight and provides for optional battery-powered operation. We believe that using the eFlow Nebulizer System to deliver ARIKAYCE will reduce treatment time and ease the patient's treatment burden and thereby potentially improve patient compliance. We believe that improved compliance with the prescribed treatment regimen may lead to a reduction in the development of antibiotic resistance by increasing the exposure of the infection to the minimum inhibitory concentration of antibiotic and therefore may ultimately lead to clinical benefit.

MANUFACTURING OF ARIKAYCE

The ARIKAYCE used in our clinical studies is manufactured for us by Ajinomoto Althea, Inc. (Althea), a third-party contract manufacturing organization in the US. We are working with Althea to develop commercial production capabilities for AIRKAYCE. Our agreement with Althea provides for a term expiring July 2014, subject to an earlier termination upon the provision of 180 days' notice by either party, or in the event of an uncured material breach, certain bankruptcy or liquidation events, or upon the occurrence of certain other specified termination events. We are negotiating with Althea to extend the manufacture of ARIKAYCE at Althea beyond July 2014. There can be no assurance that we will enter into an agreement to extend the manufacture or that we will enter into an agreement on terms favorable to us.

In February 2014, we entered into an agreement with Therapure Biopharma Inc. ("Therapure") for the manufacture of the Company's product ARIKAYCE at the larger scales necessary to support commercialization. Pursuant to the agreement, the Company and Therapure will collaborate to construct a production and quality control area for the manufacture and testing of ARIKAYCE in Therapure's existing manufacturing facility in Mississauga, Ontario, Canada. Therapure will manufacture ARIKAYCE for the Company on a non-exclusive basis. The agreement has an initial

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term of five years from the first date on which Therapure delivers ARIKAYCE to us after we obtain permits related to the manufacture of ARIKAYCE.

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

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

The eFlow nebulizer system is manufactured by PARI under the names PARI Pharma GmbH in Europe and PARI Respiratory Equipment, Inc., in the US. PARI manufactures eFlow nebulizer systems utilizing technology licensed, developed and optimized within its company and produces several commercially available eFlow technology based products for use in Europe, North America and other countries. PARI maintains facilities and equipment necessary to support manufacture of eFlow nebulizers for use with ARIKAYCE. PARI must comply with applicable governmental regulations relating to medical device production in each country of manufacture. We will continue to work with PARI to address our manufacturing needs for our clinical program and plan for commercialization. For additional information about PARI and our contractual relationships with PARI, see " License Agreements and Collaboration Agreements."

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

IPLEX

In addition to the ARIKAYCE development program, we have a second proprietary compound, IPLEX®, which is IGF-1, with its natural binding protein, IGFBP-3. IPLEX is no longer a development priority for us. We no longer have protein development capability or the in-house capability to manufacture IPLEX. Previously, under the proprietary IPLEX protein platform, we maintained an expanded access program for amyotrophic lateral sclerosis (also known as ALS or Lou Gehrig's disease) until drug supplies were exhausted at the end of 2011. It is our intention to seek licensing partners for the IPLEX development programs. In 2012, we out-licensed the IPLEX technology to Premacure Holdings AB and Premacure AB of Sweden (collectively, "Premacure") for retinopathy of prematurity indication. In March 2013, we amended the Premacure License Agreement to provide Premacure with the option to pay us $11.5 million and assume any of our royalty obligations to other parties in exchange for a fully paid license. In March 2013, Shire plc announced that they acquired Premacure. In April 2013 Shire exercised this option and paid us $11.5 million, and as a result we are not entitled to future royalties from Shire.

INTELLECTUAL PROPERTY

Patents and Trade Secrets

We own or license rights to more than 200 issued patents and pending patent applications in the US and in foreign countries, including more than 90 issued patents and pending patents related to

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

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

We monitor for activities that may infringe our proprietary rights, as well as the progression of third-party patent applications that may have the potential to create blocks to our products or otherwise interfere with the development of our business. We are aware, for example, of 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, we do not believe that our proposed products would be found to infringe any valid claim of these patents.

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

In the U.S., we own patents that, upon ARIKAYCE approval, would be listed in the FDA Orange Book that cover the ARIKAYCE composition and its use in treating lung infections, including *Pseudomonas* and NTM. Four such patents are U.S. Patent No. 7,544,369 (expires June 6, 2025), U.S. Patent No. 7,718,189 (expires June 6, 2025), U.S. Patent No. 8,226,975 (expires August 15, 2028), and U.S. Patent No. 8,632,804 (expires December 5, 2026). We also have four allowed and nine pending U.S. patent applications. Two patents have been granted by the European Patent Office and five applications are pending. Twenty nine patents have also issued in major foreign markets, e.g., Japan, China, Korea, Australia, and India, which cover ARIKAYCE and methods of using ARIKAYCE for treating lung infections. Forty one foreign patent applications are pending that cover the ARIKAYCE composition and its use in treating lung infections, including *Pseudomonas* and NTM. We anticipate that in the U.S., we will have potential patent coverage for ARIKAYCE and its use in treating lung infections, including *Pseudomonas* and NTM, through at least February 2029, which includes an additional six months of pediatric exclusivity.

In addition to the intellectual property already granted to us, we were recently informed of the following:

The U.S. Patent and Trademark Office (USPTO) granted U.S. Patent Application No. 13/527,213 for ARIKAYCE on January 21, 2014 as U.S. Patent No. 8,632,804, entitled, "Lipid-based compositions of anti-infectives for treating pulmonary infections and methods of use thereof." Once granted, it will provide exclusivity at least through December 5, 2026. This new patent will cover a method for treating a pulmonary infection, including a *Pseudomonas aeruginosa* and a mycobacterial infection, among others, in a cystic fibrosis patient, with an aerosolized pharmaceutical formulation comprising an aminoglycoside together with our

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liposomal delivery technology. Specifically, the patent will cover a method for treating a pulmonary infection in a cystic fibrosis patient comprising administering to the patient an aerosolized composition comprising ARIKAYCE.

The USPTO granted U.S. Patent Application No. 13/666,420 for ARIKAYCE on February 4, 2014 as U.S. Patent No. 8,642,075, entitled, "Lipid-based compositions of anti-infectives for treating pulmonary infections and methods of use thereof." It will provide exclusivity at least through December 5, 2026. This new patent will cover an aerosolized composition of our novel, once-daily inhalation formulation comprising amikacin and liposomal delivery technology for the treatment of pulmonary infections, including *Pseudomonas aeruginosa* and mycobacterial infections, among others.

The USPTO intends to grant U.S. Patent Application No. 13/664,181 for ARIKAYCE in a patent titled, "Lipid-based compositions of anti-infectives for treating pulmonary infections and methods of use thereof." Once granted, it will provide exclusivity at least through December 5, 2026. This new patent will cover a method for treating or providing prophylaxis against a mycobacterial infection with an aerosolized pharmaceutical formulation the patent comprising an aminoglycoside together with our liposomal delivery technology.

The USPTO intends to grant U.S. Patent Application No. 13/675,559 for ARIKAYCE on March 18, 2014 as U.S. Patent No. 8,673,348 in a patent titled, "Lipid-based compositions of anti-infectives for treating pulmonary infections and methods of use thereof." Once granted, the patent will provide exclusivity at least through December 5, 2026. This new patent will cover a method for treating a *Pseudomonas aeruginosa* infection in a patient, with an aerosolized pharmaceutical formulation comprising an aminoglycoside together with our liposomal delivery technology. Specifically, the patent will cover a method for treating a *Pseudomonas aeruginosa* infection comprising administering to the patient an aerosolized composition comprising ARIKAYCE.

The USPTO intends to grant U.S. Patent Application No. 13/675,587 for ARIKAYCE on March 18, 2014 as U.S. Patent No. 8,673,349 in a patent titled, "Lipid-based compositions of anti-infectives for treating pulmonary infections and methods of use thereof." Once granted, the patent will provide exclusivity at least through December 5, 2026. This new patent will cover a method for treating a *Burkholderia* infection in a patient, with an aerosolized pharmaceutical formulation comprising an aminoglycoside together with our liposomal delivery technology. Specifically, the patent will cover a method for treating a *Burkholderia* infection comprising administering to the patient an aerosolized composition comprising ARIKAYCE.

On September 4, 2013, the European Patent Office granted Patent No. 1909759 entitled "Sustained Release of Anti-infective Aminoglycosides" for ARIKAYCE. The granted patent provides protection for novel anti-infective formulations comprising an aminoglycoside and our liposomal delivery technology, including ARIKAYCE. The composition of matter patent provides exclusivity in all the available European Patent Office's member states, at least through July 19, 2026. The granted patent also includes claims relating to the use of the aforementioned aminoglycoside/lipid formulations for treating pulmonary infections, including those caused by Pa lung infections and certain mycobacterial infections, among others.

On October 16, 2013, the European Patent Office granted EU Patent No. 1581236, for ARIKAYCE in a patent titled, "Sustained release of anti-infectives." This patent provides exclusivity at least through October 29, 2023 in all of the available European Patent Office member states. The patent provides protection for the use of ARIKAYCE's formulation comprising amikacin and liposomal delivery technology for the treatment of pulmonary infections in CF patients. Specifically, the patent includes claims relating to the use of the aforementioned formulation for treating *Pseudomonas aeruginosa* pulmonary infections, as well as certain mycobacterial infections, among others.

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Through our agreements with PARI, we have license rights to U.S. and foreign patents and applications that cover the eFlow Nebulizer System medical device. We have rights to use the nebulizers in clinical trials and, pursuant to its agreements with us, PARI has agreed to negotiate in good faith and enter into a commercial supply agreement.

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

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

License and Collaboration Agreements

License Agreements and Other Collaboration Agreements Relating to ARIKAYCE

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

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

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

Cystic Fibrosis Foundation Therapeutics, Inc. In 2005 and 2009, we entered into research funding agreements with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) whereby we received $1.7 million and $2.2 million for each respective agreement in research funding for the development of

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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 sales milestones are met within 5 years of the drug commercialization approval in the US, we would owe an additional payment of $3.9 million.

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

License Agreements and Other Collaboration Agreements Relating to Other Compounds

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

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

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

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

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

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Trademarks

In addition to our patents and trade secrets, we have filed applications to register certain trademarks in the US and/or abroad, including INSMED, ARIKACE, ARIKAYCE, and IPLEX. At present, we have received either registration or a notice of allowance for these marks from the US Patent and Trademark Office. We have also received foreign allowances or issued foreign registrations for certain of these marks. In December 2012, we learned that the EMA had no objection to our use of the name ARIKACE. In early 2014, we learned that the FDA approved our use of the name ARIKAYCE as our proposed trade name for our liposomal amikacin for inhalation product candidate. Our ability to obtain and maintain trademark registrations will in certain geographical locations depend on making use of the mark in commerce on or in connection with our products and approval of the trademarks for our products by regulatory authorities in each country.

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 payors 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.

Major Competitors for ARIKAYCE

Our major competitors include pharmaceutical and biotechnology companies that have approved therapies or therapies in development for the treatment of chronic lung infections. Inhaled antibiotics are a standard of care in the treatment of CF to manage the chronic *Pseudomonas* infections due to the high concentrations of drug deposited directly into the lung, where the infection resides.

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

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

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

In addition, we are aware of at least two other companies, Aptalis Pharmaceuticals and KaloBios Pharmaceuticals, which have products potentially competitive to ARIKAYCE currently in development.

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

Competitor	Product/Product Candidate for Pseudomonas Lung Infections in CF Patients	Class of Product	Key Marketing Approvals	Estimated Annual Sales (millions)
Novartis	Tobi (Tobramycin Inhalation Solution or TIS)	Aminoglycoside	Europe, US and Canada	$ 387 (combined)
Novartis	Tobi Podhaler (Tobramycin Inhalation Powder or TIP)	Aminoglycoside	Europe, US and Canada	
Gilead	Cayston (Aztreonam for Inhalation Solution)	Monobactam	Europe and US	Not reported
Forest	Colomycin (Colistimethate Sodium for Inhalation)	Polymyxin	Europe	Not reported
Forest	Colobreathe (Colistimethate Sodium Powder)	Polymyxin	Europe	Not reported
Chiesi	Bramitob® and BETHKIS (Tobramycin Inhalation Solution)	Aminoglycoside	Europe and US	Not reported
Aptalis Pharmaceuticals	Aeroquin (Inhaled Levofloxacin)	Flouroquinolone	None phase 3 (data reported)	Not approved
KaloBios Pharmaceuticals	KB001-A (IV administered PEGylated mAb fragment)	Monoclonal Antibody	None phase 2 (initiated January 2013)	Not approved

We are not aware of any other companies developing an inhaled antibiotic for NTM lung infections. While there is no approved treatment for NTM lung infections, there is an American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) treatment regimen that is utilized.

GOVERNMENT REGULATION

Orphan Drugs

European Union

The EMA grants orphan drug designation to promote the development of products that may offer therapeutic benefits for life-threatening or chronically debilitating conditions affecting not more than five in 10,000 people in the EU. In addition, orphan drug designation can be granted if the drug

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is intended for a life threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that sales of the drug in the EU would be sufficient to justify developing the drug. Orphan drug designation is available either if there is no other satisfactory method approved in the EU of diagnosing, preventing or treating the condition or if a method does exist, but the proposed orphan drug will be of significant benefit to patients.

Orphan drug designation provides opportunities for free protocol assistance and fee reductions for access to the centralized regulatory procedures before and during the first year after marketing approval, which reductions are not limited to the first year after marketing approval for small and medium enterprises. In addition, if a product which has an orphan drug designation subsequently receives EMA marketing approval for the indication for which it has such designation, the product is entitled to orphan drug exclusivity, which means the EMA may not approve any other application to market the same drug for the same indication for a period of ten years. The exclusivity period may be reduced to six years if the designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Competitors may receive marketing approval of different drugs or biologics for the indications for which the orphan product has exclusivity. In order to do so, however, they must demonstrate that the new drugs or biologics provide a significant benefit over the existing orphan product. This demonstration of significant benefit may be done at the time of initial approval or in post-approval studies, depending on the type of marketing authorization granted.

United States

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

Orphan drug designation qualifies the drug sponsor for various development incentives of the ODA, including tax credits for qualified clinical testing, and a waiver of the NDA application user fee (unless the application includes an indication for other than the rare disease or condition for which the drug was designated). It also provides the potential for certain exclusivity benefits. However, it does not convey any advantage in or shorten the duration of the regulatory review and approval process, and safety and effectiveness of a drug must still be established through adequate and well-controlled studies. The first NDA applicant with FDA orphan drug designation for a particular active ingredient to actually receive FDA approval of the designated drug for the indication for which it has such designation, is entitled to a seven-year exclusive marketing period, often referred to as orphan drug exclusivity, in the US for that product and indication. During the orphan drug exclusivity period, the FDA may not approve any other applications to market the same drug for the same indication for use, except in limited circumstances, such as a showing of clinical superiority to the product that has orphan drug exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition.

Drug Approval

Europe

To obtain approval of a drug under EU regulatory systems, we may submit marketing authorizations either under a centralized or decentralized procedure. These procedures apply in the EU

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member states, plus the European Economic Area countries, Iceland, Lichtenstein, and Norway. The centralized procedure, which is compulsory for medicines produced by certain biotechnological processes and for orphan drugs and is optional for those which are highly innovative, provides for the grant of a single marketing authorization that is valid for all EU member states. Under this procedure, an applicant submits an application, including a summary of product characteristics and proposed labeling and packaging, to the reference member state and concerned member states. The reference member state prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report, each concerned member state must decide whether to approve the assessment report and related materials. If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to the public health, the disputed points may eventually be referred to the European Commission, whose decision is binding on all member states.

United States

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

Pharmaceutical product development in the US typically involves:

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

Submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin;

Approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;

Performance of adequate and well-controlled human clinical trials in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug for each indication;

Submission to the FDA of a NDA;

Satisfactory completion of an FDA advisory committee review, if applicable;

Satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and

FDA review and approval of the NDA.

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

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Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, formulation and toxicity, pharmacology, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements including good laboratory practices and 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. 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 healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with good clinical practice, or GCP, an international standard meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators, and monitors; as well as (iii) under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. subjects (patients and healthy volunteers) and subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and there are additional, more frequently reporting requirements if serious adverse events occur.

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

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap or be combined. For phase 1, the initial introduction of the drug into healthy human subjects or patients with the target disease or condition, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses and, if possible, early evidence on effectiveness. Phase 2 usually involves trials in a limited patient population with the target disease or condition to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. If a compound demonstrates evidence of effectiveness and an acceptable safety profile in phase 2 evaluations, phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed

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clinical trial sites, in order to generate enough data to statistically evaluate the drug for potential approval, to establish the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug.

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

NDA Application

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

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

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

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

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

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committed to reviewing such resubmissions in two or six months depending on the type of information included.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy and may impose other conditions, including labeling restrictions that can materially affect the potential market and profitability of the drug. The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, plan to mitigate any identified or suspected serious risks. The REMS could include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Upon NDA approval of a new chemical entity, or NCE, which is a drug that contains no active moiety that has been approved by FDA in any other NDA, that drug receives five years of marketing exclusivity during which FDA cannot receive any ANDA seeking approval of a generic version of that drug. Certain changes to a drug, such as the addition of a new indication to the package insert, are associated with a three-year period of exclusivity during which FDA cannot approve an ANDA for a generic drug that includes the change.

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

The FDCA also provides three years of marketing exclusivity for a NDA, 505(b)(2) NDA, or supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant, are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

After NDA approval, owners of relevant drug patents may apply for up to a five-year patent extension. The allowable patent term extension is calculated as half of the drug's testing phase (the time between IND application and NDA submission) and all of the review phase (the time between NDA submission and approval) up to a maximum of five years. The time can be shortened if FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years. For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the

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patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the United States Patent and Trademark Office must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which a NDA has not been submitted.

Fast Track Designation and Priority Review

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

Increasing rates of bacterial and fungal infections and resistance to current therapies, along with associated high rates of mortality, led to the 2012 passage of the Generating Antibiotic Incentives Now (GAIN) Act in the United States. The GAIN Act established incentives for the development of new therapies for serious and life-threatening infections by making streamlined priority review and fast track processes available for drugs which the FDA designates as Qualified Infectious Disease Products, or QIDPs. To qualify for designation as a QIDP according to the criteria established in the GAIN Act a product must be an antibacterial or anti-fungal drug for human use intended to treat serious or life-threatening infections, including: those caused by an anti-fungal resistant pathogen, including novel or emerging infectious pathogens; or caused by qualifying pathogens listed by the FDA in accordance with the GAIN Act.

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

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

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

Combination Products

A combination product is a product comprised of (i) two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (ii) two or more separate products

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packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (iii) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (iv) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

FDA is divided into various branches, or Centers, by product type. Different Centers typically review drug, biologic, or device applications. In order to review an application for a combination product, the FDA must decide which Center should be responsible for the review. FDA regulations require that FDA determine the combination product's primary mode of action, or PMOA, which is the single mode of a combination product that provides the most important therapeutic action of the combination product. The Center that regulates that portion of the product that generates the PMOA becomes the lead evaluator. If there are two independent modes of action, neither of which is subordinate to the other, the FDA makes a determination as to which Center to assign the product based on consistency with other combination products raising similar types of safety and effectiveness questions or to the Center with the most expertise in evaluating the most significant safety and effectiveness questions raised by the combination product. When evaluating an application, a lead Center may consult other Centers and apply the standards that would be applicable but still retain complete reviewing authority, or it may collaborate with another Center, by which the Center assigns review of a specific section of the application to another Center, delegating its review authority for that section. Typically, the FDA requires a single marketing application submitted to the Center selected to be the lead evaluator, although the agency has the discretion to require separate applications to more than one Center. One reason to submit multiple evaluations is if the applicant wishes to receive some benefit that accrues only from approval under a particular type of application, like new drug product exclusivity. If multiple applications are submitted, each may be evaluated by a different lead Center.

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

Antibiotic Exclusivity

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

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

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Disclosure of Clinical Trial Information

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

Other US Postmarketing Regulatory Requirements

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

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

Adverse event reporting and submission of periodic reports is required following FDA approval of a NDA. The FDA also may require postmarketing testing, known as phase 4 testing, risk minimization action plans and surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product.

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

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

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In addition to the potential postmarketing commitments and requirements noted above (for example, phase 4 studies, REMS) drugs manufactured or distributed pursuant to FDA approvals are subject to a broad array of extensive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

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

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

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

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Pediatric Information

European Union

For the EMA, pediatric data or an approved pediatric investigation plan, or PIP, is required to submit an MAA in the European Union. In December 2010, we received Positive Opinion of the Pediatric Committee of the EMA on the agreement of our PIP, on the granting of a deferral, and on the granting of a waiver for amikacin (sulfate) nebulizer suspension for inhalation use, in the treatment of *Pseudomonas* lung infection/colonization in CF patients in accordance with relevant European regulations. Our PIP is subject to modifications from time to time.

United States

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

Regulation Outside the US and Europe

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

Health Canada

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

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Japan

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

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

Medical Device Regulation

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

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

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

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

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

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

Reimbursement of Pharmaceutical Products

In the US, many independent third-party payers, as well as the Medicare and state Medicaid programs, reimburse buyers of pharmaceutical products. Medicare is the federal program that provides health care benefits to senior citizens and certain disabled and chronically ill persons. Medicaid is the need-based federal and state program administered by the states to provide health care benefits to certain persons. In return for including our pharmaceutical commercial products in the Medicare and Medicaid formularies, making them eligible for federally funded payments, we will need to agree to pay a rebate to state Medicaid agencies that provide reimbursement for those products. We will also have to agree to sell our commercial products under contracts with the Department of Veterans Affairs, Department of Defense, Public Health Service, and numerous other federal agencies as well as certain hospitals that are designated as 340B covered entities (entities designated by federal statutes to receive drugs at discounted prices) at prices that are significantly below the price we charge to commercial pharmaceutical distributors. These programs and contracts are highly regulated and will impose restrictions on our business. Failure to comply with these regulations and restrictions could result in a loss of our ability to continue receiving reimbursement for our drugs once approved. Medicare and Medicaid programs may also seek penalties for improper marketing, including off-label marketing, of our drugs.

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

Healthcare Law and Regulation/Fraud and Abuse Laws

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

The federal anti-kickback;

The federal civil False Claims Act;

The federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), as amended by the Health Information Technology for Economic and Clinical Health Act (HITECH), and similar state privacy laws;

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The federal criminal false statements statute;

The federal Physician Payment Sunshine Act, being implemented as the Open Payments Program; and

Analogous and similar state laws and regulations.

EMPLOYEES

As of December 31, 2013, we had a total of 61 employees, including 25 in research, clinical, regulatory and quality assurance; 18 in technical operations, manufacturing and quality control; and 18 in general and administrative functions, including pre-commercial activities. We anticipate additional hires in 2014.

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

AVAILABLE INFORMATION

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

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

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

FINANCIAL INFORMATION

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

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ITEM 1A. RISK FACTORS

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

Risks Related to Development and Commercialization of our Product Candidates

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

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

Positive results from preclinical studies of a drug candidate may not be predictive of similar results in human clinical trials, and promising results from earlier clinical trials of a drug candidate may not be replicated in later clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in earlier stages of development. Accordingly, the results of the completed clinical trials for ARIKAYCE may not be predictive of the results we may obtain in our clinical trials currently in progress or other trials. We do not expect ARIKAYCE or any other drug candidates we may develop to be commercially available for at least a year, if at all.

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

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

Identify potential drug product candidates;

Design and conduct appropriate laboratory, preclinical and other research;

Submit for and receive regulatory approval to perform clinical studies;

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Design and conduct appropriate preclinical and clinical studies according to good laboratory and good clinical practices and FDA disease-specific expectations;

Select and recruit clinical investigators;

Select and recruit subjects for our studies;

Collect, analyze and correctly interpret the data from our studies;

Submit for and receive regulatory approvals for marketing; and

Manufacture the drug product candidates and device components according to cGMP.

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

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

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

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

Our preclinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials or we may abandon projects that we expect to be promising;

Regulators or institutional review boards may prevent us from commencing a clinical trial or conducting a clinical trial at a prospective trial site;

Enrollment in the clinical trials may take longer than expected or the clinical trials as designed may not allow for sufficient patient accrual to complete enrollment of the trial;

We may decide to limit or abandon our commercial development program;

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Conditions imposed on us by the FDA or any non-US regulatory authority regarding the scope or design of our clinical trials may require us to collect and submit information to regulatory authorities, ethics committees, institutional review boards or others for review and approval;

The number of patients required for our clinical trials may be larger than we anticipate or participants may drop out of our clinical trials at a higher rate than we anticipate;

Our third party contractors, contract research organizations, which we refer to as CROs, clinical investigators, clinical laboratories, product supplier or inhalation device supplier may fail to comply with regulatory requirements or fail to meet their contractual obligations to us in a timely manner;

We may have to suspend or terminate one or more of our clinical trials if we, the regulators or the institutional review boards determine that the participants are being exposed to unacceptable health risks or for other reasons;

We may not be able to claim that a product candidate provides an advantage over current standard of care or future competitive therapies in development because our clinical studies may not have been designed to support such claims;

Regulators or institutional review boards may require that we hold, suspend or terminate clinical research for various reasons, including potential safety concerns or noncompliance with regulatory requirements;

The cost of our clinical trials may be greater than we anticipate;

The supply or quality of product used in clinical trials or other materials necessary to conduct our clinical trials may be insufficient or inadequate or we may not be able to reach agreements on acceptable terms with prospective contract manufacturers or CROs; and

The effects of our product candidates may not be the desired effects or may include undesirable side effects or the product candidates may have other unexpected characteristics.

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

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

Be delayed in obtaining, or may not be able to obtain, marketing approval for one or more of our product candidates;

Obtain approval for indications that are not as broad as intended or entirely different than those indications for which we sought approval; or

Have the product removed from the market after obtaining marketing approval.

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

We do not have any in-house manufacturing capability other than for development and characterization and depend completely on a small number of third-party manufacturers and suppliers

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for the manufacture of our product candidates on a clinical or commercial scale. ARIKAYCE and the nebulizer each are supplied by a sole manufacturer. We are dependent on Althea Technologies for the production of ARIKAYCE. We are dependent upon PARI for the production and supply of the eFlow Nebulizer System. The inability of a supplier to fulfill our supply requirements could materially adversely affect our ability to obtain and maintain regulatory approvals and future operating results. A change in the relationship with any supplier, or an adverse change in their business, could materially adversely affect our future operating results.

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

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

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. Any inability to acquire sufficient quantities of our components in a timely manner from these third parties could delay clinical trials or commercialization and prevent us from developing and distributing our products in a cost-effective manner or on a timely basis.

In addition, manufacturers of our components are subject to cGMP and similar standards and we do not have control over compliance with these regulations by our manufacturers. If one of our contract manufacturers fails to maintain compliance, the production of our products could be interrupted, resulting in delays and additional costs. In addition, if the facilities of such manufacturers do not pass a pre-approval or post-approval plant inspection, the FDA, as well as other regulatory authorities in jurisdictions outside the US, will not grant approval and may institute restrictions on the marketing or sale of our products. We are reliant on third-party manufacturers and suppliers to meet our clinical supply demands and any future commercial products. Delays in receipt of materials, scheduling, release, custom's control and regulatory compliance issues may adversely impact our ability to initiate, maintain or complete clinical trials that we are sponsoring or may adversely impact commercialization. Commercial manufacturing and supply agreements have not been established. Issues arising from scale-up, facility construction, environmental controls, equipment requirements, local and federal permits and allowances or other factors may have an adverse impact on our ability to manufacture our product candidates.

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

We have limited experience in conducting and managing the preclinical development activities and clinical trials necessary to obtain regulatory approvals, including approval by the FDA and EMA. Since our merger with Transave, we have not completed a regulatory filing 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. We have limited experience in

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conducting and managing the application process necessary to obtain regulatory approvals and we might not be able to demonstrate that our product candidates meet the appropriate standards for regulatory approval. If we are not successful in conducting and managing our preclinical development activities or clinical trials or obtaining regulatory approvals, we might not be able to commercialize ARIKAYCE, or might be significantly delayed in doing so, which may materially harm our business.

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

The completion rate of future clinical studies of our products is dependent on, among other factors, the patient enrollment rate. Patient enrollment is a function of many factors, including:

Investigator identification and recruitment;

Regulatory approvals to initiate study sites;

Patient population size;

The nature of the protocol to be used in the trial;

Patient proximity to clinical sites;

Eligibility criteria for the study;

The patients' willingness to participate in the study;

Competition from other companies' clinical studies for the same patient population; and

Ability to obtain any necessary comparator drug or medical device.

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

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 payors and others in the medical community.

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

The prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;

The efficacy and potential advantages over alternative treatments;

The pricing of our product candidates;

Relative convenience and ease of administration;

The willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;

The strength of marketing and distribution support and timing of market introduction of competitive products;

Publicity concerning our products or competing products and treatments, including competing products becoming subject to generic pricing; and

Sufficient third party insurance coverage or reimbursement.

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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 payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by more established technologies marketed by our competitors.

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

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

Risks Related to Our Reliance on Third Parties

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

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

- We may face significant competition in seeking appropriate partners;
- These arrangements are complex and time consuming to negotiate, document and implement;
- We may not be successful in our efforts to establish and implement collaborations or other alternative arrangements that we might pursue on favorable terms;
- We may not be able to effectively control whether the CROs or other third parties will devote sufficient resources to our programs or products;
- We are not able to control the regulatory compliance of CROs, third-party suppliers, contractors and collaborators;
- Disagreements with third parties and CROs may be difficult to resolve and could result in a dispute over and loss of intellectual property rights, delay or termination of the research, development, or commercialization of product candidates or result in litigation or arbitration;

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Contracts with our collaborators may fail to provide sufficient protection of our intellectual property; and

We may have difficulty enforcing the contracts if one of these collaborators fails to perform.

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

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

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

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

We are dependent upon Althea being able to provide an adequate supply of ARIKAYCE both for our clinical trials and for commercial sale in the event ARIKAYCE receives marketing approval. We do not have a long term supply agreement with Althea and are currently negotiating with Althea to extend the manufacture of ARIKAYCE at Althea beyond July 2014. There can be no assurance that we will enter into an agreement to extend the manufacture or that we will enter into an agreement on terms favorable to us. In 2013, Althea was acquired by Ajinomoto Co., a global manufacturing company based in Japan and now operates as Ajinomoto Althea, Inc.

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

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

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

Risks Related to Our Financial Condition and Capital Requirements

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

We are a biopharmaceutical company focused on developing and commercializing inhaled therapies for patients battling serious lung diseases that are often life threatening. We have incurred losses each previous year of our operation, except in 2009, when we sold our manufacturing facility and certain other assets to Merck. We expect to continue incurring operating losses for the foreseeable future. The process of developing and commercializing our products requires significant pre-clinical and clinical testing as well as regulatory approvals for commercialization and marketing before we are allowed to begin product sales. In addition, commercialization of our drug candidates likely would require us to establish a sales and marketing organization and contractual relationships to enable product manufacturing and other related activities. We expect that our activities, together with our general and administrative expenses, will continue to result in substantial operating losses for the foreseeable future. As of December 31, 2013, our accumulated deficit was $391.6 million. For the year ended December 31, 2013, our consolidated net loss was $56.1 million.

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

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

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

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

Our operations have consumed substantial amounts of cash since our inception. We expect to continue to incur substantial research and development expenses, and we expect to expend substantial financial resources to complete development of, seek regulatory approval for, and prepare for commercialization of ARIKAYCE. We may need to seek additional funding in order to complete any clinical trials related to ARIKAYCE, seek regulatory approvals of ARIKAYCE, and commercially launch ARIKAYCE. We also may require additional future capital in order to continue our other research and development activities or to acquire complementary technology. As of December 31, 2013, we had $113.9 million of cash and cash equivalents and a certificate of deposit on hand. If adequate funds are not available to us when needed, we may be required to reduce or eliminate research and development programs or commercial efforts.

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

Phase 2 and phase 3 clinical trials and commercialization of ARIKAYCE;

Non-clinical and clinical testing;

Process development and scale up for manufacturing;

Manufacturing;

Performance of our third-party suppliers and manufacturers;

Obtaining marketing, sales and distribution capabilities;

Obtaining regulatory approvals;

Research and development, including formulation development;

Retaining employees and consultants;

Filing and prosecuting patent applications and enforcing patent claims;

Establishing strategic alliances and collaborations with third-parties; and

Current and potential future litigation.

We also may need to spend more funds than currently expected because we may further change or alter drug development plans, acquire additional drugs or drug candidates or we may misjudge our costs. As of December 31, 2013, we had no committed sources of capital and do not know whether additional financing will be available when needed, or, if available, that the terms will be favorable. We cannot assure that our cash reserves together with any subsequent funding will be sufficient for our capital requirements. The failure to satisfy our capital requirements will adversely affect our business, financial condition, results of operations and prospects.

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

We currently have no meaningful source of revenue.

In 2013, we generated other revenue from the modification of a previously granted license of our IPLEX technology. In 2012, we generated no revenue. In 2011, we generated revenue from our expanded access program, or EAP, and the license of certain technology to a third party. Unless we can execute one or more revenue generating transactions or successfully obtain regulatory approval for and commercialize ARIKAYCE, we will have no material sources of operating revenue. We expect to continue to incur substantial additional operating losses for at least the next several years as we continue to develop and seek to commercialize ARIKAYCE.

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

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

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

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

In process research and development (IPRD) currently comprises approximately 33% of our total assets. A reduction in the value of our IPRD could impact our results of operations.

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

We may be unable to use our net operating losses.

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

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Risks Related to Regulatory Matters

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

We are required to obtain various regulatory approvals prior to studying our products in humans and then again before we market and distribute our products. The regulatory review and approval processes in both the US and Europe require evaluation of preclinical studies and clinical studies, as well as the evaluation of our manufacturing process. These processes are complex, lengthy, expensive, resource intensive and uncertain. Securing regulatory approval to market our products requires the submission of much more extensive preclinical and clinical data, manufacturing information regarding the process and facility, scientific data characterizing our product and other supporting data to the regulatory authorities in order to establish its safety and effectiveness. This process also is complex, lengthy, expensive, resource intensive and uncertain. We have limited experience in submitting and pursuing applications necessary to gain these regulatory approvals.

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

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

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

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

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

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

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

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

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

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

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

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

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Changes to the approved product, product labeling or manufacturing process;

Advertising and other promotional material; and

Disclosure of clinical trial results on publicly available databases.

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

State wholesale drug distribution laws and the distribution of our product samples to physicians must comply with the requirements of the Prescription Drug Marketing Act;

Sales, marketing and scientific or educational grant programs must comply with the anti-kickback and fraud and abuse provisions of the Social Security Act, the transparency provision of the Patient Protection and Affordable Care Act and an associated reconciliation bill that became law in March 2010, which we refer to collectively as the Health Care Reform Law, federal and state patient privacy laws, the False Claims Act and similar state laws; and

Pricing and rebate programs must comply with the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990 and the Veteran's Health Care Act of 1992, and if products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply.

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

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

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

Issue warning letters or untitled letters asserting that we are in violation of the law;

Seek an injunction or impose civil or criminal penalties or monetary fines;

Suspend or withdraw marketing approval;

Suspend any ongoing clinical trials;

Refuse to approve pending applications or supplements to applications submitted by us;

Suspend or impose restrictions on operations, including costly new manufacturing requirements;

Seize or detain products, refuse to permit the import or export of products, or require us to initiate a product recall;

Refuse to allow us to enter into supply contracts, including government contracts;

Impose civil monetary penalties; or

Pursue civil or criminal prosecutions and fines against our company or responsible officers.

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

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

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

Regulatory authorities may withdraw their approval of the product;

Regulatory authorities may require the addition of labeling statements, such as black box or other warnings or contraindications;

Regulatory authorities may require us to issue specific communications to healthcare professionals, such as "Dear Doctor Letters;"

Regulatory authorities may impose additional restrictions on marketing and distribution of the products;

Regulatory authorities may issue negative publicity regarding the product, including safety communications;

We may be required to change the way the product is administered, conduct additional clinical studies or restrict the distribution of the product;

We could be sued and held liable for harm caused to subjects;

We could be subject to negative publicity; and

Our reputation may suffer.

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

If we are unable to obtain adequate reimbursement from governments or third-party payors 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 payors, both in the US and in other markets. Reimbursement by a third party payor may depend upon a number of factors, including the third party payor'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 payor 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 payor. 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 payors' satisfaction. Such studies might require us to commit a significant amount of management time and financial and other resources. Even when a payor determines that a product is eligible for

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

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

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

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

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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 adversely affect our revenue and results of operations.

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

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

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

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

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

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

We may enter into collaborative relationships that would involve our collaborators conducting proprietary development programs. Any conflict with our collaborators could limit our ability to obtain

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future collaboration agreements and negatively in