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 reporte