INSMED INC
Form 10-K
March 13, 2012

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2011

OR

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

For the transition period from _____ to _____

Commission File Number 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 Capital 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 o No þ

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 o No þ

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 þ No o

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 þ No o

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 2I of this Form 10-K or any amendment to this Form 10-K. þ

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 o Accelerated filer þ Non-accelerated filer o Small Reporting Company o

Indicate by check mark whether the registrant is a shell Company (as defined in Rule 12b-2 of the Exchange Act). Yes o No þ

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant on [date], was [$] (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 that all of its directors, officers and persons owning 10% or more of the outstanding Common Stock are affiliates. This assumption shall not be deemed conclusive for any other purpose.

On March 9, 2012, there were 24,863,771 shares of the registrant's common stock, $.01 par value, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for its 2012 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission no later than 120 days, or April 30, 2012, after the registrant's fiscal year ended December 31, 2011, and to be delivered to shareholders in connection with the 2012 Annual Meeting of Shareholders, are herein incorporated by reference in Part III of this Form 10-K.

INSMED INCORPORATED

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In this Form 10-K, we use the words the “Company,” “Insmed,” “Insmed Incorporated,” “we,” “us” and “our” to refer to Insme
Incorporated, a Virginia corporation. [Insmed], ARIKACE 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

Statements contained herein, including without limitation, “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” contain certain projections, estimates and other forward-looking statements. “Forward-looking statements,” as that term is defined in the Private Securities Litigation Reform Act of 1995, 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,” “con similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements.

Forward-looking statements include, but are not limited to: our ability to develop ARIKACE®; 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 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 U.S. Food and Drug Administration (the “FDA”); 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 collaborators with acceptable development, regulatory and commercialization expertise; the benefits to be derived from corporate collaborations, license agreements and other collaborative efforts, including those relating to the development and commercialization of our product candidates; sources of revenues and anticipated revenues, including contributions from corporate collaborations, license agreements and other collaborative 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 manufacturing capacity for our product candidates.

Forward-looking statements are based upon our current expectations and beliefs. Our actual results and the timing of certain events may differ materially from the results discussed, projected, anticipated or indicated in any forward-looking statements. Any forward-looking statement should be considered in light of 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 and in any other documents incorporated by reference. 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 Incorporated is a development-stage biopharmaceutical company with expertise in proprietary, advanced liposomal technology designed specifically for inhalation lung delivery. We develop innovative inhaled treatments for serious lung infections. Our proprietary liposomal technology is designed specifically for delivery of pharmaceuticals to the lung, and we believe it provides for potential improvements to the conventional inhalation methods of delivering drug to the pulmonary system. These potential advantages include improvements in efficacy, safety and patient convenience. Our primary focus is on orphan markets with high unmet medical needs, which we believe presents a significant opportunity, as their challenge and complexity best fit our knowledge, know-how and expertise.

Our strategy is to utilize our patented advanced liposomal technology to develop safe and effective medicines that improve upon standards of care for those orphan respiratory diseases in which patient needs are currently unmet. Our initial primary target indications are Pseudomonas aeruginosa, which we refer to as Pseudomonas, lung infections in cystic fibrosis (CF) patients and patients with non-tuberculous mycobacteria (NTM) lung infections.

We completed a business combination with Transave, Inc., or Transave, on December 1, 2010, which we refer to as the "Merger," a privately-held, NJ-based pharmaceutical company focused on the development of differentiated and innovative inhaled pharmaceuticals for the site-specific treatment of serious lung infections. Our integration with Transave was completed in 2011 including the relocation of corporate headquarters to Monmouth Junction, New Jersey, and cessation of operations at the Richmond, Virginia, location as of December 31, 2011. On March 2, 2011, we completed a one-for-ten reverse stock split of our common stock. Unless otherwise noted, the per share amounts in this 10-K give retroactive effect to the reverse stock split for all periods presented.

Immediately after giving effect to the Merger, former Transave stockholders owned approximately a 46.7% equity interest in the combined company (on an as-converted, fully diluted basis), and legacy Insmed shareholders had a 53.3% equity interest. The shares retained by us pursuant to the merger agreement with Transave (approximately 1.76 million shares of common stock after giving effect to the conversion of the Series B Conditional Convertible Preferred Stock, or Series B Preferred Stock, and the one-for-ten reverse stock split of our common stock) will be delivered on June 12, 2012 to certain former Transave stockholders, subject to reduction for any claims and indemnification payments that are pending.

Development Program

Our lead product candidate, ARIKACE® (liposomal amikacin for inhalation), is a differentiated, inhaled antibiotic supported by positive Phase 2 results for treating serious lung infections due to susceptible bacteria. ARIKACE is considered a New Chemical Entity (NCE) by the United States (U.S.) Food and Drug Administration, or FDA, primarily due to its patented liposomal technology. However, the key active ingredient, amikacin, is already an FDA-approved antibiotic with proven efficacy in the treatment of gram-negative infections including Pseudomonas. ARIKACE is in the aminoglycoside class of antibiotics.

We believe that ARIKACE has potential usage in at least two orphan indications with high unmet need: CF patients who have Pseudomonas lung infections and patients who have NTM lung infections. We estimate the global market potential for these two orphan indications combined to be up to $1 billion.

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For CF patients, we believe ARIKACE has the potential to be differentiated from other marketed drugs for the treatment of chronic Pseudomonas lung infections due to its ability to deliver high, sustained levels of amikacin directly to the lung, potentially providing sustained improvement in lung function and improvement in patient symptoms with only a once-a-day dosing regimen. In Phase 2 clinical studies, ARIKACE was shown to improve lung function both during and between treatment periods in patients with CF. If approved for CF, ARIKACE could potentially be the first inhaled antibiotic to be approved for once-daily administration. For NTM patients, we believe that ARIKACE has the potential to fulfill a growing, significant unmet medical need.

We have been granted orphan drug designation for CF patients who have Pseudomonas lung infections in both the United States (U.S.) and the EU. We applied for orphan drug designation for NTM infections in the U.S. in 2011. In response to this application, the FDA has requested either in vivo or clinical data in support of our application for orphan drug designation. We plan to file for orphan drug designation for NTM lung infections in the EU after obtaining additional pre-clinical data, which is expected by the end of 2012.

In August 2011, we announced that the FDA had placed a clinical hold on our Phase 3 clinical trials for ARIKACE in CF patients with Pseudomonas lung infections and for patients with NTM lung infections. Since the clinical programs were being conducted under separate INDs, we received separate notifications for CF and NTM. A clinical hold is a notification issued by the FDA to the sponsor to delay a proposed clinical trial or suspend an ongoing clinical trial. The FDA informed us that this decision was based on an initial review of the results of a long-term rat inhalation carcinogenicity study with ARIKACE. As part of the study, rats were given ARIKACE daily by inhalation for almost two years. Two of the 120 rats receiving the highest dose had a single lung tumor. These rats received ARIKACE doses that are much greater than the doses to be administered to humans. The relevance of the observed rat tumors to the use of ARIKACE in humans is unknown. ARIKACE was not associated with changes that may lead to tumors in shorter-term studies that we conducted in other animals. Additionally, in a standard series of tests that we performed, ARIKACE was not shown to be genotoxic. The FDA requested additional information on ARIKACE and data from the rat study. As a result of the clinical hold, we suspended initiation of the ARIKACE Phase 3 clinical trial programs, including the recruitment and enrollment of patients.

We provided the requested information to the FDA in August and was informed by the FDA that, based on its review of the information provided to date, including the rat inhalation carcinogenicity study results, the FDA had insufficient information to assess the risks for ARIKACE in CF patients. In October 2011, the FDA notified us that the FDA was continuing the clinical hold previously placed on our Phase 3 clinical trial for ARIKACE in CF patients with Pseudomonas lung infections and in patients with NTM lung infections. Regarding the clinical hold for CF patients with Pseudomonas lung infections, the FDA requested additional information from us, including that we conduct a nine-month dog inhalation toxicity study of ARIKACE to determine if the findings of the rat inhalation carcinogenicity study are also observed in a non-rodent model and to propose a CF patient population/disease state in which the risk-benefit profile of ARIKACE may be more favorable. We were informed during further dialogue with the FDA that if we chose to proceed, the required nine-month dog inhalation toxicity study of ARIKACE could be conducted in parallel with the CF Phase 3 clinical trials in human subjects. Regarding the clinical hold for patients with NTM lung infections, the FDA requested we conduct a Phase 2 clinical trial in adult (age 18 and older) NTM patients to provide proof-of-concept efficacy and safety data for ARIKACE in NTM patients.

In January 2012, the FDA lifted the clinical hold on ARIKACE in patients with NTM lung infections. We intend to conduct, as requested by the FDA, a Phase 2 clinical trial in adult NTM patients to provide proof-of-concept efficacy and safety data for ARIKACE in NTM patients. We expect to begin enrolling patients in the Phase 2 clinical trial in mid-2012. We have also begun the work required to allow the Company to initiate the nine-month dog inhalation toxicity study in the second quarter of 2012.

In February 2012, we filed our complete response to the FDA clinical hold on the U.S. study of ARIKACE in CF patients with Pseudomonas infection. We will continue discussions with the FDA to pursue removal of the clinical hold on ARIKACE in U.S. for the treatment of CF patients with Pseudomonas lung infections.

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We are moving forward with the ARIKACE clinical development program in CF in Europe. The European study in CF patients with Pseudomonas lung infections will be a randomized, phase 3 trial comparing ARIKACE 560 mg, delivered once daily via an optimized, investigational eFlow® Nebulizer System (PARI Pharma GmbH, Munich, Germany), to TOBI®(1) (inhaled tobramycin solution), which is a marketed inhaled antibiotic that is delivered twice daily. The Company anticipates that the study will be conducted in approximately 300 patients. The primary endpoint will be change in pulmonary function (FEV-1) measured after three 28 day on-treatment and three 28 day off-treatment cycles (about six months). A key secondary endpoint will be time to pulmonary exacerbation. The study design was previously agreed upon by Insmed and the European Medicines Agency. Eligible patients will have the option to participate in a longer term open-label safety study. The Company expects to begin enrolling patients in the phase 3 European clinical study in the second quarter of 2012.

Our current priorities are as follows.

- Initiate a European Phase 3 pivotal clinical trial for ARIKACE in the treatment of CF patients with Pseudomonas lung infections with initial patient enrollment expected in the second quarter of 2012;

- Initiate a U.S. Phase 2 clinical trial in patients with NTM lung infections with initial patient enrollment expected in mid-2012;

- Continue discussions with FDA to attempt to remove the clinical hold on ARIKACE in U.S. for the treatment of CF patients with Pseudomonas lung infections; and

- Initiate a nine-month dog inhalation toxicity study in the second quarter of 2012.

In addition to the ARIKACE development program, we have a secondary proprietary compound, IPLEX®, which is no longer a development priority for us. We no longer have protein development capability nor the in-house capability to manufacture IPLEX. We announced in January 2012 that we intend to seek licensing partners for the IPLEX development programs. Under the proprietary IPLEX protein platform, we maintained an expanded access program until drug supplies were exhausted at the end of 2011 for amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. We also have provided IPLEX for an early-stage research program investigating retinopathy of prematurity (ROP) through an IPLEX Material Transfer Agreement with Premacure AB, a private company located in Sweden. Sufficient quantity of IPLEX has been supplied to Premacure for its completion of an ongoing Phase 2 trial, which Premacure will conduct and analyze at its expense.

ARIKACE Overview

We believe that our lead product candidate, ARIKACE,has the potential to be differentiated from other marketed drugs for the treatment of chronic lung infections due to its ability to deliver high, sustained levels of amikacin directly to the lung and to minimize the serum levels of amikacin compared with IV administration. We believe the inhalation delivery of amikacin provided by ARIKACE may improve efficacy and may reduce the potential to cause adverse events such as ototoxicity (hearing loss, ringing in the ears and/or loss of balance) and nephrotoxicity (toxicity to the kidneys) compared with intravenous administration. In addition, ARIKACE may be more convenient to administer as it is delivered once daily compared with the currently marketed inhaled antibiotics, which require administration two to three times daily.

We believe that ARIKACE has the potential to be differentiated further because the liposomal delivery technology may allow ARIKACE to reach the site of the lung infection better than other inhaled aminoglycoside antibiotics. For treating Pseudomonas lung infections in CF patients, ARIKACE was designed with a neutrally charged liposome and has been shown, in vitro (or in laboratory studies), to penetrate the negatively charged bacterial biofilm, a protective

barrier produced by Pseudomonas. While all aminoglycoside antibiotics are positively charged and bind to the negative surface of the biofilm, only ARIKACE has been shown to penetrate the biofilm effectively. This means that ARIKACE may reach the site of the Pseudomonas infection in CF patients' lungs more efficiently than the other aminoglycoside antibiotics.

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For NTM lung infections, ARIKACE has been shown to be preferentially taken up by the macrophages, where NTM often grows. As NTM is an intracellular pathogen, this may allow ARIKACE to reach the site of the NTM lung infections better than other antibiotics.

Development Summary: Treatment of Pseudomonas Lung Infections in CF Patients

In Phase 2 studies in CF patients with Pseudomonas lung infections, ARIKACE has been shown to provide improvement in lung function during treatment and sustained improvement in lung function between treatment periods. If approved, ARIKACE could be the first approved inhaled antibiotic to be administered once daily.

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. We completed two randomized, placebo-controlled phase 2 studies with ARIKACE in 105 CF patients who had chronic Pseudomonas lung infections. Data from the patients receiving the target Phase 3 program dose of ARIKACE, 560 mg, is summarized below. ARIKACE was delivered at a dose of 560 mg once daily via an eFlow Nebulizer System for 28 consecutive days. ARIKACE demonstrated statistically significant and clinically meaningful improvement in lung function throughout the 28-day 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 (days 29 through 56) and was statistically significantly better than placebo.

In a follow-on separate long-term, open-label, multi-cycle clinical trial conducted in Europe, ARIKACE was given at a dose of 560 mg via an eFlow Nebulizer System (to patients for six complete cycles). (Open label means that both the patient and the treating physician know that they are receiving ARIKACE and not placebo.) Each cycle 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, ARIKACE produced an improvement in lung function that was sustained over the six cycles (approximately 17 months). In addition, during the off-treatment periods, 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, ARIKACE 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, ARIKACE was well-tolerated with overall adverse events reported as consistent with those expected in a population of CF patients receiving inhaled medicines.

We currently expect to commence patient accrual in the second quarter of 2012 for a Phase 3 clinical study of ARIKACE for CF patients with Pseudomonas lung infections to support potential approval in Europe and potentially other countries outside the U.S. The study will be a randomized, Phase 3 trial comparing ARIKACE 560 mg, delivered once daily via an optimized, investigational eFlow Nebulizer System, to Tobi®(1) (inhaled tobramycin solution, Novartis Pharmaceutical Corporation), which is a marketed inhaled antibiotic that is delivered twice daily. We anticipate that the study will be conducted in approximately 300 patients. The primary endpoint will be change in pulmonary function (FEV-1) measured after three 28 day on-treatment and three 28 day off-treatment cycles (about six months). A key secondary endpoint will be time to pulmonary exacerbation. The study design was previously agreed upon by us and the European Medicines Agency (EMA).

The key elements of these study designs and regulatory paths have been agreed to with the EMA and with the regulatory agencies in the individual countries in which the trials will be conducted.

In February 2012, we filed our complete response to the FDA clinical hold on the U.S. study of ARIKACE in CF patients with Pseudomonas infection. We will continue discussions with the FDA to pursue removal of the clinical hold on ARIKACE in U.S. for the treatment of CF patients with Pseudomonas lung infections.

Development Summary: Treatment of Patients with NTM Lung Infections

In the NTM indication, we filed an IND application and gained agreement from the FDA in the first quarter of 2011 to conduct a Phase 3 clinical trial in patients with NTM lung infections. In August 2011, we announced that the FDA had placed the ARIKACE clinical trial program for patients with NTM lung infections on hold. In January 2012, the FDA lifted the clinical hold on the ARIKACE clinical trial program for NTM.

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On February 9, 2012, we announced that we were proceeding with initiation of patient accrual to a Phase 2, placebo-controlled trial for adult patients who have lung infections due to NTM. This NTM trial differs in two ways from the trial that was agreed to by us and the FDA before the clinical hold was put into place: (1) the current trial is considered a Phase 2 trial rather than a Phase 3 trial, and (2) the current trial will be conducted in adult patients (ages 18 and above) rather than patients who are ages 12 and above.

The Phase 2 clinical trial for ARIKACE in NTM patients will consist of a randomized, placebo-controlled study of approximately 100 adult patients with recalcitrant NTM lung infections. There are two parts to the study: a randomized portion and an open-label portion. Patients who are NTM culture positive will continue with their antibiotic treatment regimen, and receive additionally, either ARIKACE 560 mg, delivered once daily via an optimized, investigational eFlow Nebulizer System, or placebo once daily. The primary efficacy endpoint will be change in mycobacterial density from baseline to the end of 84 days of treatment. At the conclusion of the randomized portion of the study, eligible patients will receive ARIKACE 560 mg once daily for an additional 84 days in an open-label design, primarily to measure longer-term safety and efficacy. The clinical trial design was previously agreed upon by us and the FDA. We expect to begin enrolling patients in the Phase 2 clinical trial in mid-2012.

Patients enrolled in the study will include those with NTM lung infections with persistently positive mycobacterial cultures following a stable ATS/IDSA-guidelines-based treatment regimen defined as “adherent to a multi-drug regimen for at least 6 months prior to screening.” Only patients who have non-TB Mycobacterium Avium Complex (MAC) or non-TB Mycobacterium Abscessus will be permitted to enroll in the trial. These are two sub-types of NTM that are believed to account for the vast majority of NTM lung infections in the U.S.

Overall Product Profile

The overall product profile that we are working to develop for ARIKACE includes: (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 Pseudomonas 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; (3) reduced dosing frequency; and (4) decreased administration time.

ARIKACE Delivery Technology

There are two separate components to the delivery technology for ARIKACE. There is the liposomal formulation of the drug and the device, a nebulizer through which ARIKACE is inhaled through the mouth into the lung.

The liposomal formulation is key to both the retention of amikacin in the lung, which allows once-a-day dosing, and the ability of ARIKACE to gain close access to bacteria (Pseudomonas aeruginosa) 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 allows high concentrations of drug to be delivered where it is needed most to improve efficacy.

Liposomes are microscopic spherical shells that contain water surrounded by a thin lipid membrane. ARIKACE liposomes are less than 0.3 microns in diameter and contain amikacin in the water interior in a very high concentration; they are very efficient delivery systems that have been optimized for inhalation therapy. These liposomes are formed using neutral lipids identical to those found naturally in the lung; therefore the composition is highly compatible with lung tissue.

With a neutral surface charge and small size, ARIKACE liposomes are able to effectively penetrate the thick CF mucus and the bacteria’s protective covering (biofilm), both of which we believe restrict the availability of unencapsulated aminoglycosides such as tobramycin and amikacin. ARIKACE liposomes are also readily taken up by

immune cells in the lung (alveolar macrophages) that “eat” inhaled particles. When NTM infects these immune cells, it is usually sheltered against attack from external antibiotics, but with ARIKACE, the uptake of the liposomes allows the drug to get inside these cells to attack the organisms.

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The second part of our technology is the state-of-the-art drug delivery nebulizer, which we believe represents a competitive advantage. ARIKACE will be administered once daily via inhalation using an investigational eFlow Nebulizer System optimized specifically for ARIKACE. We believe the optimized, investigational eFlow Nebulizer System significantly reduces treatment time, thereby easing the patient's treatment burden and potentially improving patient compliance.

The patented optimized, investigational eFlow Nebulizer System is a medical device that uses eFlow technology to enable highly efficient aerosolization, or delivery of inhaled medication, including liposomal formulations via a vibrating, perforated membrane that includes thousands of specially designed laser-drilled holes, which aids the delivery of ARIKACE to the lung. We believe that compared with current nebulizer systems, the optimized, investigational eFlow Nebulizer System is significantly more efficient because it 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. Combined with its quiet mode of operation, small size, light weight and battery-powered operation, we believe the optimized, investigational eFlow Nebulizer System potentially reduces the burden of taking daily inhaled treatments.

Market Opportunity Summary

ARIKACE

Our current intention is to retain marketing rights for ARIKACE in the U.S. We will continue to evaluate our marketing options for Europe and other countries. Because of the small focused nature of the potential physician prescribing population for CF and NTM patients in the U.S., we believe ARIKACE will require limited commercial infrastructure (e.g., fewer than 50 sales representatives in the U.S.), which may enable us to achieve profitability sooner following market launch than an indication that requires a much larger internal commercial infrastructure.

Market Opportunity: CF Patients with Pseudomonas Lung Infections

CF is an inherited chronic disease that is often diagnosed before the age of two. According to the Cystic Fibrosis Foundation, CF affects roughly 30,000 children and adults in the U.S. and roughly 70,000 children and adults worldwide. Among other issues, CF causes a thick, sticky mucous to develop in and clog the lungs creating an ideal environment for various pathogens, such as Pseudomonas, to form and grow, infecting the lung and leading to inflammation and loss of lung function.

According to the Cystic Fibrosis Foundation Patient Registry (2010), despite extensive treatment with multiple antibiotics, improved nutrition, and other treatments, life expectancy of a CF patient is only about 38 years. A recent study reported in the Journal of Cystic Fibrosis (2010) found that deterioration in lung function is the main cause of death in these patients and despite best efforts, lung function declines by 1% to 3% annually with some patients experiencing an annual decline of 10% or more.

According to the Cystic Fibrosis Foundation (Cystic Fibrosis Foundation Patient Registry, 2010), more than half of all CF patients acquired Pseudomonas lung infections by age 18. Patients generally receive extensive antibiotic treatments, which can be delivered via the oral, intravenous and inhaled routes. Antibiotics delivered via inhalation have become part of standard treatments for CF patients with Pseudomonas lung infections and are generally thought to be a way to deliver more drug directly to the site of infection compared with other routes of administration. However, in part because of the thick sticky mucous these patients produce in their lungs, CF patients seldom clear the Pseudomonas permanently from their lungs and become chronically infected in spite of all currently available antibiotic treatments.

CF therapy significantly impacts patients' quality of life. Some patients with CF spend up to three hours per day taking medications and other treatments, including inhaled antibiotics. The current most commonly used inhaled antibiotic in the U.S. is inhaled tobramycin (Tobi), which was approved by the FDA and has been sold in the U.S. since January 1998. Tobi is administered twice daily over 30 to 40 minutes per day 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 ARIKACE will be administered once daily for approximately 13 minutes per day for 28 days followed by 28-day off-drug period. We believe that any inhaled treatment that reduces the treatment burden of a CF patient could represent a significant improvement in the patient's quality of life. We believe a once-daily shorter treatment could foster better compliance and potentially result in better effectiveness. We have been granted orphan drug designation for CF patients who have Pseudomonas lung infections in both the U.S. and the EU.

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Because current marketed inhaled antibiotics do not produce an improvement in lung function as measured by Forced Expiratory Volume in one second (FEV-1) that lasts during the 28-day-off treatment periods, CF thought leaders have begun to recommend more aggressive inhaled antibiotic treatment for CF patients by using a different class of inhaled antibiotic in the off period with the goal of better maintaining lung function. Aminoglycosides, including Tobi, are recommended as first-line inhaled antibiotic treatment in the on-month due to their established effectiveness against Pseudomonas. If the effectiveness of ARIKACE against Pseudomonas is confirmed after the evaluation of Phase 3 data and ARIKACE is approved, our goal is for ARIKACE also to be recommended as first-line inhaled antibiotic treatment in the on-month.

We believe that the global CF market for inhaled antibiotics will experience significant growth in the next five to ten years from the approximately $450 to $500 million market today. This growth is being driven by physicians' desire to maintain CF patients' lung function, which continues to decline in many patients despite extensive treatment with current therapies including the currently approved inhaled antibiotics.

Expected growth in the market is due to:

- Physicians moving to alternating regimens every month as opposed to giving patients off-treatment holidays on alternate months;

- Better patient adherence to physician prescribed regimens resulting from more convenient (less frequent and less time consuming) treatments

- Physicians initiating inhaled antibiotics earlier for patients with Pseudomonas in their lungs;

- CF patients living longer; and

- The standard of care in the rest of the world continuing to advance closer to that of the EU and the U.S.

Market Opportunity: NTM Lung Infections

NTM lung infections can cause severe pulmonary disease for which there are currently limited effective treatments. NTM are organisms common in soil and water that have been associated with lung disease in select patient groups. NTM may be considered to be a cousin of tuberculosis (TB) but not contagious. Many people have NTM in their bodies, but it does not normally cause a problem and lead to an infection, as it is believed the body's self-regulating immune system usually successfully combats the threat of NTM infection. It is not completely understood why some individuals are susceptible to NTM infections. However, the patients affected often are immune-compromised or have structural damage in their lungs at the time they become infected.

Mycobacteria are intracellular organisms that invade and multiply chiefly within macrophages. They are characteristically resistant to most antibiotics. NTM lung infections usually are chronic conditions that can lead to frequent exacerbations and lengthy hospital stays. Treatment for NTM lung infections requires lengthy multi-drug regimens that can be poorly tolerated and poorly effective, especially in patients with severe disease or in those who have failed prior treatment attempts. There have been very few clinical trials to support current treatment recommendations, and no new drugs have been assessed for this disease in many years.

According to a Company-sponsored analysis conducted by SDI Healthcare, more than 30,000 patients visited physician offices suffering with NTM lung infections in the U.S. during 2008. There were between 14,000 and 15,000 patients who had a hospital visit for a primary diagnosis of NTM. The average age of these patients was about 66. Approximately two-thirds of the NTM patients received at least one antibiotic and of those receiving an

antibiotic, they received between seven and eight courses in 2008.

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Although there are many species of nontuberculous mycobacteria that have been reported to cause lung infections, ARIKACE will be used to treat two of the most common, Mycobacterium Avium Complex (MAC) and Mycobacterium abscessus. MAC accounts for the vast majority of NTM lung infections with prevalence rates from 72% to over 85% in the U.S. The reported prevalence rates for M. Abscessus range from 3% to 11% in the U.S. The diagnosed prevalence of NTM species causing lung infections varies geographically with lower rates of MAC reported in Europe in the 25% to 55% range.

We believe the unmet need for new therapies in the treatment of NTM lung infections is very high. Patients are often treated with the same antibiotics that are used to treat TB. Current treatment usually consists of lengthy multi-drug antibiotic regimens that are often poorly tolerated and not very effective, especially in patients with severe disease or in those who have failed prior treatments. Treatment guidelines published in 2007 in the American Journal of Respiratory and Critical Care Medicine report that few clinical trials are under way to identify treatment recommendations, and no new antibiotics have been studied for the treatment of NTM lung infections in multi-center, randomized clinical trials for many years.

Amikacin is not approved by the FDA for NTM lung infections but is often recommended as part of the standard treatment regimen for some NTM patients. It is delivered mostly via intravenous administration but sometimes via inhalation. As the drug is delivered for months at a time, there can be considerable toxicity associated with treatment due to the high systemic (blood) levels of the drug, which can lead to ototoxicity (hearing loss, ringing in the ears and/or loss of balance) and nephrotoxicity (toxicity to the kidneys).

We believe that ARIKACE may be effective in treating patients with NTM lung infections because of the ability of the ARIKACE liposomes to be taken up inside lung macrophages that harbor invading organisms such as NTM. Macrophages are immune cells whose primary function includes removing foreign particles and bacteria from the lungs. Ironically, NTM organisms “hide” within the macrophages, making treatment difficult as drugs cannot efficiently gain access to the macrophage interior. Because ARIKACE liposomes are recognized as foreign particles, they are also internalized by the macrophages, consequently delivering very high levels of drug inside the macrophages to reach the NTM bacteria. In addition, we believe that the depot effect of ARIKACE in the lung and lower level of systemic exposure compared to intravenous amikacin may provide additional benefits to these patients and reduce the ototoxicity and nephrotoxicity.

We applied for orphan drug designation for NTM infections in the U.S. in 2011. In response to our application, the FDA has requested either in vivo (non-clinical data in animals) or clinical data in support of our application for orphan drug designation. We plan to file for orphan drug designation for NTM lung infections again the U.S. and in the EU after obtaining additional pre-clinical data.

Additional Market Opportunity: Non-CF Bronchiectasis Patients with Pseudomonas aeruginosa Lung Infections

While we are concentrating our development efforts on the areas we believe have the greatest potential, the treatment of Pseudomonas lung infections in CF patients and patients with NTM lung infections, we believe that ARIKACE has potential to be used for treating other types of conditions. We may pursue additional areas of development once we have completed clinical studies for the first two indications. We believe non-CF bronchiectasis offers another potential market opportunity and that ARIKACE has the potential to be used to treat non-CF bronchiectasis characterized by Pseudomonas lung infections, for which we also have orphan drug status in the U.S.

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 in these patients. Patients evolve to a chronic inflammation-infection cycle. Disease burden has primarily been linked to productive cough and high levels of sputum (lung mucus) production.

It is estimated that approximately 30% of non-CF bronchiectasis patients are infected with Pseudomonas. When bronchiectasis patients become infected with Pseudomonas, they tend to have more frequent exacerbations and hospitalizations and are more frequent users of antibiotics.

While we believe there is a significant opportunity to develop ARIKACE for non-CF bronchiectasis, we do not intend to initiate further clinical studies until we have completed additional clinical studies for the first two indications, CF patients with Pseudomonas lung infections and NTM lung infections. At that time, we will evaluate whether to develop ARIKACE further for this potential indication.

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IPLEX

We have a proprietary protein product, IPLEX (mecaserminrinfabate, recombinant DNA origin, injection), a complex of recombinant human IGF-1 and its binding protein IGFBP-3 (rhIGF-1/rhIGFBP-3). IPLEX has been studied as a treatment for several serious medical conditions such as myotonic muscular dystrophy (MMD) and ALS. It is currently being evaluated in the treatment of retinopathy of