

INSMED Inc
Form 424B2
August 13, 2014

Filed Pursuant to Rule 424(b)(2)

Registration No. 333-196418

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered	Proposed Maximum Offering Price per Share	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee(1)
Common Stock, par value \$0.01 per share	10,235,000	\$ 11.25	\$ 115,143,750	\$ 14,830.52

(1) Calculated pursuant to Rule 457(r) of the Securities Act of 1933, as amended.

PROSPECTUS SUPPLEMENT

(To Prospectus dated May 30, 2014)

8,900,000 Shares

Common Stock

We are offering up to 8,900,000 shares of our common stock.

Our common stock is listed on The NASDAQ Global Select Market under the symbol INSM. The last reported sale price of our common stock on The NASDAQ Global Select Market on August 12, 2014 was \$11.81 per share.

Investing in our common stock involves a high degree of risk. See Risk Factors beginning on page S-5 of this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	Per Share		Total	
Public offering price	\$	11.25	\$	100,125,000
Underwriting discounts and commissions(1)	\$	0.675	\$	6,007,500
Proceeds, before expenses, to us	\$	10.575	\$	94,117,500

(1) We have agreed to reimburse the underwriters for certain expenses in connection with this offering. See Underwriting.

The underwriters also may purchase up to an additional 1,335,000 shares of our common stock at the public offering price, less the underwriting discounts and commissions payable by us, within 30 days from the date of this prospectus supplement. If the underwriters exercise this option in full, the total underwriting discounts and commissions will be \$6,908,625 and our total proceeds, after underwriting discounts and commissions but before expenses, will be \$108,235,125.

The underwriters are offering the common stock as set forth under **Underwriting**. Delivery of the shares will be made on or about August 18, 2014.

Sole Book-Running Manager

Leerink Partners

Lead Managers

Piper Jaffray

JMP Securities

Co-Manager

H.C. Wainwright & Co., LLC

Prospectus Supplement dated August 12, 2014

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Prospectus

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus relate to a registration statement that we filed with the Securities and Exchange Commission, or SEC, using a shelf registration process. Both this prospectus supplement and the accompanying prospectus include or incorporate by reference important information about us, our common stock and other information you should know before investing in our common stock. You should read both this prospectus supplement and the accompanying prospectus as well as the additional information described under **Where You Can Find More Information** in this prospectus supplement before making an investment decision.

We have not authorized any dealer, agent or other person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus supplement and the accompanying prospectus and any related free writing prospectus we may authorize to be delivered to you. You must not rely upon any information or representation not contained or incorporated by reference in this prospectus supplement or the accompanying prospectus or in any related free writing prospectus authorized by us. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the common stock offered hereby, nor do this prospectus supplement and the accompanying prospectus constitute an offer to sell or the solicitation of an offer to buy securities, in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction. You should not assume that the information contained in this prospectus supplement and the accompanying prospectus is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus supplement and any accompanying prospectus is delivered or securities are sold on a later date.

This prospectus supplement may add to, update or change the information in the accompanying prospectus and the documents incorporated by reference herein. If information in this prospectus supplement is inconsistent with information in the accompanying prospectus or any document incorporated by reference, this prospectus supplement will apply and will supersede that information in the accompanying prospectus or in the document incorporated by reference.

Unless otherwise indicated or unless the context requires otherwise, all references in this prospectus supplement to **Insmed**, the **Company**, **we**, **us** and **our** refer to Insmed Incorporated, together with its consolidated subsidiaries. **ARIKACE** and **IPLEX** are registered trademarks of Insmed Incorporated and **Insmed** and **ARIKAYCE** are trademarks of Insmed Incorporated. Our logos and trademarks are the property of Insmed. All other brand names or trademarks appearing in this prospectus are the property of their respective holders. Use or display by us of other parties' trademarks, trade dress, or products in this prospectus supplement is not intended to, and does not, imply a relationship with, or endorsements or sponsorship of, us by the trademark or trade dress owners.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information included or incorporated by reference in this prospectus supplement and the accompanying prospectus and does not contain all of the information that may be important to you. You should carefully review this entire prospectus supplement and the accompanying prospectus, including the risk factors and financial statements included and incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision to purchase our common stock.

BUSINESS OVERVIEW

Insmed is a biopharmaceutical company currently 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.

In March 2014, we reported top-line clinical results from the double-blind portion of our phase 2 clinical trial in the United States (US) and Canada of ARIKAYCE in patients who have lung infections caused by nontuberculous mycobacteria (NTM) (Study 112). The randomized, double-blind, placebo-controlled phase 2 clinical trial compared ARIKAYCE (590 mg delivered once daily), added to standard of care treatment, versus standard of care treatment plus placebo, in 90 adult patients with treatment resistant NTM lung disease. Eligibility for the study required patients to have been on the American Thoracic Society/Infectious Disease Society of America guideline therapy for at least six months prior to screening and to continue to have persistently positive mycobacterial cultures. The primary efficacy endpoint of the study was a semi-quantitative measurement of the change in mycobacterial density on a seven-point scale from baseline (day one) to the end of the randomized portion of the trial (day 84). ARIKAYCE did not meet the pre-specified level for statistical significance although there was a positive trend ($p=0.148$) in favor of ARIKAYCE. However, ARIKAYCE did achieve statistical significance with regard to the clinically relevant key secondary endpoint of culture conversion, with 11 out of 44 patients treated with ARIKAYCE (added to standard of care treatment) demonstrating clearance of the infecting mycobacterial organism (culture negative) by day 84 of the study as compared to 3 out of 45 patients treated with placebo (added to standard of care treatment) ($p=0.01$).

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

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

In August 2014, we announced that, following discussions with European regulatory authorities, we intend to file by the end of 2014 a Marketing Authorization Application (MAA) with the EMA for ARIKAYCE for the treatment of NTM lung infections in treatment refractory patients as well as for *Pseudomonas aeruginosa* (*Pseudomonas*) lung infections in cystic fibrosis (CF) patients.

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In August 2014, we announced that we plan to initiate a phase 3 study which will be designed to confirm, in as short a timeframe as possible, the positive culture conversion results seen in the phase 2 study, primarily investigating ARIKAYCE for use in the treatment refractory population with *mycobacterium avium* complex (MAC) NTM lung infections. This subgroup of the phase 2 trial's patients responded particularly strongly to the

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treatment. We also announced that we will proceed with our previously planned phase 3 study of the effectiveness of ARIKAYCE for the treatment of lung infections in the broad NTM population. These decisions followed a meeting with the FDA in which the FDA indicated that further exploration of the effectiveness of ARIKAYCE is appropriate before filing a new drug application (NDA) and acknowledged that exploration of the effectiveness of ARIKAYCE in a broader population is appropriate, based on the results of the recently conducted phase 2 trial, which showed statistically significant negative culture conversion in patients refractory to standard therapy.

While we intend to use the results from these two studies as the basis for future NDA and supplemental NDA (sNDA) filings, it is possible that FDA may find the study design or the results of the two Phase 3 trials inadequate to support such filings. However, we believe this two-trial approach will enable both the rapid confirmation of the previous study results to provide the quickest path to filing, as well as expansion of the potential overall label for approval. Following discussions with the FDA, both trials will focus on culture conversion as the primary measure of efficacy, and we anticipate that the studies will provide us with longer term culture conversion data to establish the sustainability of the culture conversions. We also believe that the trials will provide additional safety data to supplement the filing with the FDA for ARIKAYCE. We expect results from the smaller confirmatory study in the first half of 2016 and results for the larger trial in 2017. We cannot predict the outcome of these trials or whether our decision to conduct these trials or the data generated from the trials will impact the review of our anticipated filings for marketing approval with the EMA.

The CF and NTM target indications address orphan patient populations. Our strategy includes plans to continue to develop ARIKAYCE in the NTM patient population 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 US, Europe, Canada and Japan. We anticipate that if approved, ARIKAYCE would be the first once-a-day inhaled antibiotic treatment option available for the CF indication and the NTM indication. The following table summarizes the current status of ARIKAYCE development.

Product Candidate/Target Indications	Status	Next Expected Milestones
	<ul style="list-style-type: none"> •We reported top-line clinical results from our phase 2 clinical trial which stated that ARIKAYCE did not meet the pre-specified level for statistical significance with respect to the primary endpoint, but did achieve statistical significance with regard to the clinically relevant key secondary endpoint of culture conversion. •Results collected from the open label phase show that 21 of these patients were culture negative for NTM at Day 168. •Granted Orphan Drug designation in Europe and the US. •Granted QIDP designation, which includes Priority Review, by the FDA. •Granted Fast Track designation by the FDA which permits a rolling submission of an NDA. 	<ul style="list-style-type: none"> •We intend to file by the end of 2014 a MAA with the EMA for the treatment of NTM lung infections in treatment refractory patients as well as for <i>Pseudomonas</i> lung infections in CF patients. •We will proceed with our previously planned phase 3 study of the effectiveness of ARIKAYCE for the treatment of lung infections in the broad NTM population. •We also plan to initiate a second phase 3 study which will be designed to confirm, in as short a timeframe as possible, the positive culture conversion results seen in the phase 2 study. This confirmatory study will primarily investigate ARIKAYCE for use in the treatment refractory population with MAC NTM lung infections. •If approved, we expect ARIKAYCE would be the first approved inhaled antibiotic treatment for NTM lung infections.

ARIKAYCE Non-tuberculous
mycobacteria (NTM) lung infections

•Granted Breakthrough Therapy designation
for ARIKAYCE in the US in June 2014
based upon the

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	<p>culture conversion results in the phase 2 clinical trial.</p>	<ul style="list-style-type: none"> •We are developing plans to commercialize ARIKAYCE, if approved, in certain countries in Europe and in the US, and eventually Canada, Japan and certain other countries including Korea, Taiwan and China.
	<ul style="list-style-type: none"> •Reported top-line results from our phase 3 clinical trial conducted in Europe and Canada, in which once-daily ARIKAYCE achieved its primary endpoint of non-inferiority when compared to twice-daily tobramycin inhaled solution. •Conducting a two-year, open-label safety study in patients who completed the phase 3 clinical trial. We expect to complete this study in mid-2015. •Reported top-line results from the first group of patients who completed the first year of the two-year open label extension study. 	<ul style="list-style-type: none"> •We intend to file a MAA with the EMA by the end of 2014 and in Canada during the first half of 2015. •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 <i>Pseudomonas</i> lung infections in CF patients. •We currently do not plan to initiate any further studies in <i>Pseudomonas</i> lung infections.
ARIKAYCE <i>Pseudomonas aeruginosa</i> lung infections in CF patients	<ul style="list-style-type: none"> •Granted orphan drug designation in Europe and the US. 	
ARIKAYCE <i>Pseudomonas aeruginosa</i> and other susceptible organisms causing lung infections in non-CF bronchiectasis patients	<ul style="list-style-type: none"> •Completed phase 2 study in the US. •Granted orphan drug designation in the US. 	<ul style="list-style-type: none"> •We currently do not intend to initiate further clinical studies with respect to a non-CF bronchiectasis indication.

Amikacin sulfate is an FDA-approved antibiotic with proven efficacy in the treatment of a broad range of gram-negative infections, including *Pseudomonas* and NTM. ARIKAYCE is in the aminoglycoside class of antibiotics. We believe there currently is no drug approved in Europe or the US for treatment of NTM lung infections, and as a result all current drug treatments for NTM are used off-label. If approved for NTM patients, we believe 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 believe ARIKAYCE would be the first inhaled antibiotic to be approved for once-daily administration in this indication. ARIKAYCE has been granted orphan drug designations in the following indications:

- 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.

THE OFFERING

Common stock offered by us	8,900,000 shares.
Common stock to be outstanding after this offering	48,176,389 shares.
Use of proceeds	We intend to use the net proceeds from this offering to fund further clinical development of ARIKAYCE for NTM patients and <i>Pseudomonas</i> in CF patients, to fund our efforts to obtain regulatory approvals and commercialize ARIKAYCE for NTM patients and <i>Pseudomonas</i> in CF patients, to invest in increased third-party manufacturing capacity in anticipation of possible commercial launch of ARIKAYCE in Europe and the United States, and the balance to fund working capital, capital expenditures, general research and development, and other general corporate purposes, which may include the acquisition or in-license of additional compounds, product candidates, technology or businesses.
Risk Factors	An investment in our common stock involves a high degree of risk. See Risk Factors beginning on page S-5 of this prospectus supplement, as well as the sections entitled Risk Factors contained in the accompanying prospectus and in our Annual Report on Form 10-K for the year ended December 31, 2013 and our subsequent quarterly reports on Form 10-Q, incorporated by reference in this prospectus supplement and the accompanying prospectus, before deciding to invest in shares of our common stock.
Option to purchase additional shares	We have granted the underwriters have an option for a period of 30 days from the date of this prospectus supplement to purchase up to 1,335,000 additional shares of our common stock.
NASDAQ Global Select Market symbol	Our common stock is listed on the NASDAQ Global Select Market under the symbol INSM .
Participation by certain officers and directors	Certain of our officers and directors have agreed to purchase an aggregate of 88,889 shares of common stock in this offering at the public offering price.

The number of shares of our common stock to be outstanding after this offering is based on 39,276,389 actual shares of our common stock outstanding as of June 30, 2014.

The number of shares of our common stock to be outstanding after this offering excludes:

- 5,058,459 shares of our common stock issuable upon the exercise of stock options outstanding as of June 30, 2014 at a weighted average exercise price of \$10.42 per share; and
- 20,960 shares of our common stock issuable pursuant to unvested restricted stock units outstanding as of June 30, 2014 at a weighted average grant price of \$19.35.

Unless otherwise stated, all information in this prospectus supplement assumes no exercise by the underwriters of their option to purchase additional shares.

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RISK FACTORS

An investment in our common stock involves significant risks. Before making an investment in our common stock, you should carefully read all of the information contained in this prospectus supplement, the accompanying prospectus and in the documents incorporated by reference herein. For a discussion of risk factors that you should carefully consider before deciding to purchase any of our common stock, please review the risk factors Item 1A. Risk Factors in our Annual Report on Form 10-K for the year ended December 31, 2013 and our subsequent quarterly reports on Form 10-Q as well as the additional risk factors disclosed below. In addition, please read *About This Prospectus Supplement* and *Forward-Looking Statements* in this prospectus supplement, where we describe additional uncertainties associated with our business and the forward-looking statements included or incorporated by reference in this prospectus supplement and the accompanying prospectus. Please note that additional risks not currently known to us or that we currently deem immaterial also may adversely affect our business, results of operations, financial condition and prospects.

Risks Related to Development and Commercialization of our Product Candidates

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

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

Positive results from preclinical studies of a drug candidate may not be predictive of similar results in human clinical trials, and promising results from earlier clinical trials of a drug candidate may not be replicated in later clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in earlier stages of development. Accordingly, the results of the completed clinical trials for ARIKAYCE may not be predictive of the results we may obtain in future or ongoing clinical trials. On March 26, 2014, we reported top-line clinical results from a phase 2 clinical trial in the US and Canada of ARIKAYCE in patients who have lung infections caused by NTM. ARIKAYCE did not meet the pre-specified level for statistical significance with respect to the primary endpoint although there was a positive trend ($p=0.148$) in favor of ARIKAYCE.

On August 4, 2014 we announced that we intend to file by the end of 2014 a MAA with the EMA for ARIKAYCE for the treatment of NTM lung infections in treatment refractory patients as well as for *Pseudomonas* lung infections in CF patients.

In addition we also announced that we plan to initiate two phase 3 studies of the effectiveness and safety of ARIKAYCE for the treatment of lung infections in the treatment refractory and broad NTM populations, respectively. We believe that the trials will provide additional safety data to supplement the filing with the FDA and address any questions the FDA may have about ARIKAYCE's safety profile.

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

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

Our long-term viability and growth depend on the successful commercialization of ARIKAYCE and potentially other product candidates that lead to revenue and profits. Pharmaceutical product development is an

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expensive, high risk, lengthy, complicated, resource intensive process. In order to conduct the development programs for our products, we must, among other things, be able to successfully:

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

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

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

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

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

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

- The supply or quality of product used in clinical trials or other materials necessary to conduct our clinical trials may be insufficient or inadequate or we may not be able to reach agreements on acceptable terms with prospective contract manufacturers or CROs; and
- The effects of our product candidates may not be the desired effects or may include undesirable side effects or the product candidates may have other unexpected characteristics.

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

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

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

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

We do not have any in-house manufacturing capability other than for development and characterization and depend completely on a small number of third-party manufacturers and suppliers for the manufacture of our product candidates on a clinical or commercial scale. ARIKAYCE and the nebulizer each are supplied by a sole manufacturer. We are dependent on Althea Technologies for the production of ARIKAYCE. We are dependent upon PARI for the production and supply of the eFlow Nebulizer System. The inability of a supplier to fulfill our supply requirements could materially adversely affect our ability to obtain and maintain regulatory approvals and future operating results. A change in the relationship with any supplier, or an adverse change in their business, could materially adversely affect our future operating results.

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

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

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

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

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

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

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

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

- Investigator identification and recruitment;
- Regulatory approvals to initiate study sites;
- Patient population size;
- The nature of the protocol to be used in the trial;
- Patient proximity to clinical sites;
- Eligibility criteria for the study;
- The patients' willingness to participate in the study;

- Competition from other companies clinical studies for the same patient population; and
- Ability to obtain any necessary comparator drug or medical device.

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

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

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

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

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

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

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

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into arrangements with third parties to sell ARIKAYCE on favorable terms or at all. In the event we are unable to develop our own marketing and sales force or collaborate with a third-party marketing and sales organization, we may not be able to successfully commercialize ARIKAYCE or any other product candidates that we develop, which would adversely affect our ability to generate product revenues. Further, whether we commercialize products on our own or rely on a third party to do so, our ability to generate revenue will be dependent on the effectiveness of the sales force.

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Risks Related to Our Reliance on Third Parties

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

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

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

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

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

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

In July 2014, we entered into a Commercialization Agreement with PARI, referred to herein as the Commercialization Agreement, for the manufacture and supply of nebulizers and related accessories, referred to herein as the Device, as optimized for use with our proprietary liposomal amikacin for inhalation. The Commercialization Agreement has an initial term of fifteen years from the first commercial sale of the Device. The

term of the Commercialization Agreement may be extended by the Company for an additional five years by providing written notice to PARI at the least one year prior to the expiration of such initial term. Notwithstanding the foregoing, the parties have certain rights and obligations under the Commercialization Agreement prior to the commencement of the initial term. The Commercialization Agreement allows for termination by either party upon the occurrence of certain events, including (i) the material breach by the other party of any provision of the Commercialization Agreement, (ii) the default or bankruptcy of the other party, or (iii) upon termination by the Company of the License Agreement between the parties.

In the event PARI terminates the license agreement or Commercialization Agreement and ceases to manufacture the nebulizer, we cannot be certain that we would be able identify another willing supplier for the nebulizer on terms we require. A disruption in the supply of nebulizers could delay, impair, or prevent the development and commercialization of our products and adversely affect our business, financial condition, results of operations and prospects.

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

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

Althea currently manufactures ARIKAYCE at a relatively small scale. In order to meet potential commercial demand, if ARIKAYCE is approved, we have entered into a Contract Manufacturing Agreement with Therapure Biopharma Inc. (Therapure) for the manufacture of the Company's product ARIKAYCE. Therapure may not be able to successfully transfer the ARIKAYCE manufacturing process to their site, or we may not be able to obtain regulatory approvals for ARIKAYCE produced at Therapure's facility. We may not be able to secure an alternative source of ARIKAYCE at an adequate scale of production.

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

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

Risks Related to Our Financial Condition and Capital Requirements

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

We are a biopharmaceutical company focused on developing and commercializing inhaled therapies for patients battling serious lung diseases that are often life threatening. We have incurred losses each previous year of our operation, except in 2009, when we sold our manufacturing facility and certain other assets to Merck. We expect to continue incurring operating losses for the foreseeable future. The process of developing and commercializing our products requires significant pre-clinical and clinical testing as well as regulatory approvals for commercialization and marketing before we are allowed to begin product sales. In addition, commercialization of our drug candidates

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likely would require us to establish a sales and marketing organization and contractual relationships to enable product manufacturing and other related activities. We expect that our activities, together with our general and administrative expenses, will continue to result in substantial operating losses for the foreseeable future. As of June 30, 2014, our accumulated deficit was \$429.1 million. For the six months ended June 30, 2014, our consolidated net loss was \$37.5 million.

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

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

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

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

Our operations have consumed substantial amounts of cash since our inception. We expect to continue to incur substantial research and development expenses, and we expect to expend substantial financial resources to complete development of, seek regulatory approval for, and prepare for commercialization of ARIKAYCE. We will need to seek additional funding in order to complete any clinical trials related to ARIKAYCE, seek regulatory approvals of ARIKAYCE, and commercially launch ARIKAYCE. We also may require additional future capital in order to continue our other research and development activities or to acquire complementary technology. As of June 30, 2014, we had \$82.7 million of cash and cash equivalents and a certificate of deposit on hand. If adequate funds are not available to us when needed, we may be required to reduce or eliminate research and development programs or commercial efforts.

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

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

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- Non-clinical and clinical testing;
- Process development and scale up for manufacturing;
- Manufacturing;
- Performance of our third-party suppliers and manufacturers;
- Obtaining marketing, sales and distribution capabilities;

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- Obtaining regulatory approvals;
- Research and development, including formulation development;
- Retaining employees and consultants;
- Filing and prosecuting patent applications and enforcing patent claims;
- Establishing strategic alliances and collaborations with third-parties; and
- Current and potential future litigation.

We also may need to spend more funds than currently expected because we may further change or alter drug development plans, acquire additional drugs or drug candidates or we may misjudge our costs. As of June 30, 2014, we had no committed sources of capital and do not know whether additional financing will be available when needed, or, if available, that the terms will be favorable. We cannot assure that our cash reserves together with any subsequent funding will be sufficient for our capital requirements. The failure to satisfy our capital requirements will adversely affect our business, financial condition, results of operations and prospects.

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

We currently have no meaningful source of revenue.

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

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

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

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

Our loan agreement with Hercules contains various restrictive covenants, including restrictions on our ability to incur additional debt, transfer or place a lien or security interest on our assets, including our intellectual property, merge with or acquire other companies, redeem or repurchase any shares of our capital stock or pay cash dividends to our stockholders. The Loan Agreement also contains certain other covenants (including limitations on other indebtedness, liens, acquisitions, investments and dividends), and events of default (including payment defaults, breaches of covenants following any applicable cure period, a material impairment in the perfection or priority of the lender's security interest or in the collateral, and events relating to bankruptcy or insolvency). Upon

the occurrence of an event of default, a default interest rate of an additional 5% may be applied to the outstanding loan balances, and the lender may terminate its lending commitment, declare all outstanding obligations immediately due and payable, and take such other actions as set forth in the Loan Agreement. In addition, pursuant to the Loan Agreement, the lender has the right to participate, in an amount of up to \$1.0 million, in certain future private equity financing(s). Our borrowings under the Loan Agreement are secured by a lien on our assets, excluding our intellectual property, and in the event of a default on the loan, the lender may have the right to seize our assets securing our obligations under the Loan Agreement. The terms and restrictions provided for in the Loan Agreement may inhibit our ability to conduct our business and to provide distributions to our stockholders. Future debt securities or other financing arrangements could contain negative covenants similar to, or even more restrictive than, the Hercules loan.

In process research and development (IPRD) currently comprises approximately 39% of our total assets. A reduction in the value of our IPRD could impact our results of operations.

As a result of the merger with Transave we recorded an intangible IPRD asset of \$77.9 million and goodwill of \$6.3 million on our balance sheet. As a result of our clinical hold announced in late 2011 we recorded a charge of \$26.0 million in the fourth quarter of 2011 and reduced the value of IPRD to \$58.2 million and reduced goodwill to zero. Other potential future activities or results could result in additional write-downs of IPRD, which would adversely affect our results of operations.

We may be unable to use our net operating losses.

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

Risks Related to Regulatory Matters

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

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

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

required for review of any application for regulatory agency approval of a particular product.

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

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

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

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

FDA may base accelerated approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint (other than survival or irreversible morbidity). FDA regulations referred to as Subpart H Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses describe the potential use of surrogate endpoints. A surrogate endpoint used for accelerated approval is a marker a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality. The FDA bases its decision on whether to accept the proposed surrogate or intermediate clinical endpoint on the scientific support for that endpoint. Studies that demonstrate a drug's effect on a surrogate or intermediate clinical endpoint must be adequate and well controlled as required by the Federal Food, Drug and Cosmetic Act. The results reported in March 2014 for our phase 2 clinical trial for ARIKAYCE for NTM illustrate the challenges relating to endpoint selection.

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

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

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

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

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

- Labeling, such as black box or other warnings or contraindications;
- Post-market surveillance, post-market studies or post-market clinical trials;
- Packaging, storage, distribution, safety surveillance, advertising, promotion, recordkeeping and reporting of safety and other post-market information;
- Monitoring and reporting adverse events and instances of the failure of a product to meet the specifications in the NDA;
- Changes to the approved product, product labeling or manufacturing process;
- Advertising and other promotional material; and
- Disclosure of clinical trial results on publicly available databases.

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

- State wholesale drug distribution laws and the distribution of our product samples to physicians must comply with the requirements of the Prescription Drug Marketing Act;
- Sales, marketing and scientific or educational grant programs must comply with the anti-kickback and fraud and abuse provisions of the Social Security Act, the transparency provision of the Patient Protection and Affordable Care Act and an associated reconciliation bill that

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became law in March 2010, which we refer to collectively as the Health Care Reform Law, federal and state patient privacy laws, the False Claims Act and similar state laws; and

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

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

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

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

- Issue warning letters or untitled letters asserting that we are in violation of the law;
- Seek an injunction or impose civil or criminal penalties or monetary fines;
- Suspend or withdraw marketing approval;

- Suspend any ongoing clinical trials;
- Refuse to approve pending applications or supplements to applications submitted by us;
- Suspend or impose restrictions on operations, including costly new manufacturing requirements;
- Seize or detain products, refuse to permit the import or export of products, or require us to initiate a product recall;
- Refuse to allow us to enter into supply contracts, including government contracts;
- Impose civil monetary penalties; or
- Pursue civil or criminal prosecutions and fines against our company or responsible officers.

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

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

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

- Regulatory authorities may withdraw their approval of the product;
- Regulatory authorities may require the addition of labeling statements, such as black box or other warnings or contraindications;

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

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

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

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

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

Obtaining reimbursement approval for a product from each government or other third-party payor is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost effectiveness data for the use of our products to each payor. We may not be able to provide data sufficient to gain acceptance with respect to reimbursement or we might need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to such payors' satisfaction. Such studies might require us to commit a significant amount of management time and financial and other resources. Even when a payor determines that a product is eligible for reimbursement, the payor may impose coverage limitations that preclude payment for some uses that are approved by the FDA or non-US regulatory authorities. In addition, there is a risk that full reimbursement may not be available for high priced products. Moreover, eligibility for coverage does not imply that any product will be reimbursed in all cases or at a rate that allows us to make a profit or even cover our costs. Interim payments for new products, if applicable, also may not be sufficient to cover our costs and may not be made permanent. Subsequent approvals of competitive products could result in a detrimental change to the reimbursement of our products.

There is a significant focus in the US healthcare industry and elsewhere on cost containment. We expect changes in the Medicare program and state Medicaid programs, as well as managed care organizations and other third-party payors to continue to put pressure on pharmaceutical product pricing. In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and

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introduced a new reimbursement methodology based on average sales prices for drugs. In addition, this legislation authorized Medicare Part D prescription drug plans to use formularies where they can limit the number of drugs that will be covered in any therapeutic class. As a result of this legislation and the expansion of federal coverage of drug products, we expect that there will be additional pressure to contain and reduce costs. These cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products and could seriously harm our business. Although the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations when setting their own reimbursement rates, and any reimbursement reduction resulting from the MMA may result in a similar reduction in payments from private payors.

In March 2010, the Patient Protection and Affordable Care Act, or PPACA, which was intended to broaden access to health insurance, constrain and reduce the growth of healthcare spending, enhance remedies against fraud

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

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

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

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

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

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

Any trade name we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the US Patent and Trademark Office, or PTO. The FDA typically conducts a rigorous review of proposed trade names, including an evaluation of potential for confusion with other trade names and medication error. The FDA also may object to a trade name if it believes the name is inappropriately promotional. The FDA approved our use of the name ARIKAYCE as our proposed trade name for our liposomal amikacin for inhalation product candidate. Even after the FDA approves a trade name, the FDA may request that we adopt an

alternative name for the product if adverse event reports indicate a potential for

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confusion with other trade names and medication error. If we are required to adopt an alternative name, the commercialization of ARIKAYCE could be delayed or interrupted, which would limit our ability to commercialize ARIKAYCE and generate revenues. In December 2012, we learned that the EMA had no objection to our request to use the names ARIKACE or ARIKAYCE.

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

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

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

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

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

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

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

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services. Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including fines or exclusion or suspension from federal and state health care programs such as Medicare and Medicaid and debarment from contracting with the U.S. government. In addition, private individuals have the ability to bring actions on behalf of the government under the federal False Claims Act as well as under the false claims laws of several states.

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

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

Risks Related to Our Intellectual Property

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

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

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

Even if issued, patents issued to us or our licensors may be challenged, narrowed, invalidated, held to be unenforceable or circumvented, which could limit our ability to stop competitors from marketing similar products or reduce the term of patent protection we may have for our products. We cannot assure you that any patents obtained will afford us adequate protection or provide us with any meaningful competitive advantages against these competitors. Currently, our European Patent No. 1909759 is being opposed by a third party.

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

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

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

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

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

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

Third parties may claim that we have infringed upon or misappropriated their proprietary rights. Third parties may attempt to obtain, patent protection relating to the production and use of our product candidates. We cannot assure you that any issued patents, or patents that may later issue to third parties, would not negatively affect our commercialization of ARIKAYCE or any other product. We cannot assure you that such patents can be avoided or invalidated or would be licensed to us at commercially reasonable rates or at all. We cannot assure you that we will be successful in any intellectual property litigation that may arise or that such litigation would not have an adverse effect on our business, financial condition, results of operation or prospects. In the event of a successful claim against us for infringement or misappropriation of a third party's proprietary rights, we may be required to:

- Pay damages, including up to treble damages, and the other party's attorneys' fees, which may be substantial;
- Cease the development, manufacture, marketing and sale of products or use of processes that infringe the proprietary rights of others;

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

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

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

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

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

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

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

Risks Related to Our Industry

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

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

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

In each of our potential product areas, we face substantial competition from large pharmaceutical, biotechnology and other companies, universities and research institutions. Relative to us, most of these entities have substantially greater capital resources, research and development staffs, facilities and experience in conducting clinical studies and obtaining regulatory approvals, as well as in manufacturing and marketing pharmaceutical products. Many of our competitors may achieve product commercialization or patent protection earlier than us. Furthermore, we believe that our competitors have used, and may continue to use, litigation to gain a competitive advantage. Finally, our competitors may use different technologies or approaches to the development of products similar to the products we are seeking to develop.

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

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

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

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

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

FDA approval of products that treat the underlying cause of CF could reduce the market opportunity for ARIKAYCE.

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The FDA and EMA have approved Kalydeco (ivacaftor) by Vertex as the first drug approved to treat patients with certain mutations of CF, which affects about 4% of CF patients. Vertex also is studying Kalydeco, in combination with another drug candidate, for a more common CF mutation. We cannot predict the potential effects of Kalydeco or similar products approved in the future on inhaled antibiotic use in CF. It is possible that these therapies could decrease the number or proportion of CF patients who acquire *Pseudomonas* lung infections and thereby decrease the market for inhaled antibiotics like ARIKAYCE.

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

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the US. See Business Government Regulation Orphan Drugs United States. The company that obtains the first marketing approval from the FDA for a designated orphan drug for a rare disease receives marketing exclusivity for use of that drug for the designated condition for a period of seven years. Similar laws exist in EU with a term of ten years. See

Business Government Regulation Orphan Drugs Europe. If a competitor obtains approval of the same drug for the same indication or disease before us, we would be prohibited from obtaining approval for our product for seven or more years, unless our product can be shown to be clinically superior. In addition, more than one drug may be approved by the FDA for the same orphan indication or disease as long as the drugs are different drugs. As a result, even if one of our products is approved and receives orphan drug exclusivity, as ARIKAYCE was for treating CF patients with *Pseudomonas*, the FDA may approve different drugs for use in treating the same indication or disease covered by our product, which could adversely affect our competitive position.

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

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

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

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

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

Risks Related to Employee Matters and Managing Growth

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

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

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

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

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

We expect that our potential expansion into areas and activities requiring additional expertise, such as further clinical trials, governmental approvals, manufacturing, sales, marketing and distribution will place additional requirements on our management, operational and financial resources. Future growth would impose significant added responsibilities on members of management, including the need to identify, recruit, maintain, motivate and integrate additional employees. Also, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees.

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

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

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

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

- Our listing status on the Nasdaq Global Select Market;

- Results of our clinical studies and preclinical studies, or those of our corporate partners or our competitors;

- Delays in timing of pre-clinical, clinical development and regulatory filings and delays regarding our inability to obtain potential approvals;

- Strategic business decisions;

- Developments in our relationships with corporate partners;

- Developments affecting our corporate partners;
- Negative regulatory action or regulatory approval with respect to our announcement or our competitors' announcements of new products;
- Government regulation, reimbursement changes and governmental investigation or audits related to us or to our products;
- Developments related to our patents or other proprietary rights or those of our competitors;
- Other competitive developments;
- Reports issued by and changes in the position of securities analysts with respect to our stock or changes in stock ownership by investors;
- Operating results below the expectations of securities analysts and investors; and
- The need or perceived need to raise additional capital.

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

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

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

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The sale of a significant number of shares of our common stock in the public market could harm the market price of our common stock. Some or all of the shares of common stock may be offered from time to time in the open market pursuant to Rule 144 (or pursuant to a registration statement, if one is effective), and these sales may have a depressive effect on the market for the shares of common stock. In general, a person who is deemed to be an affiliate who has held shares for a period of six months may, upon filing of a notification on Form 144 with the SEC, sell into the market common stock in an amount up to the greater of 1% of the outstanding shares or the average weekly number of shares sold in the last four weeks before such sale. Such sales may be repeated once each three months. A non-affiliate holding restricted shares may sell such shares without restrictions after they have been held six months, subject only to the current public information requirement. After an additional six months have lapsed, a non-affiliate may sell such shares without any restrictions.

The market price for our common stock could also decline, perhaps significantly, as a result of issuances of a large number of shares of our common stock in the public market or even the perception that such issuances could occur. For example, at the time of our merger with Transave, certain former Transave stockholders holding approximately 40% of our shares of common stock as of December 1, 2010, entered into lock-up arrangements with us in connection with the merger. The lock-up arrangements expired on May 30, 2012, and these shareholders may now generally dispose of all their shares freely except to the extent that any such shareholder is an affiliate of the Company.

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

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

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

As of June 30, 2014, 5,079,419 shares of our common stock are potentially issuable under outstanding restricted stock units and stock options to our employees, officers, directors and consultants.

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

Additionally, our Articles of Incorporation currently authorize us to issue up to 500 million common shares. As of June 30, 2014 we had 39,276,389 shares of common stock outstanding. To the extent that we issue additional common stock in connection with any offerings of securities, strategic transactions, or otherwise, the ownership interest of existing shareholders will be further diluted.

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

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

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

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

- A provision allowing us to issue preferred stock with rights senior to those of the common stock without any further vote or action by the holders of the common stock. The issuance of preferred stock could decrease the amount of earnings and assets available for distribution to the holders of common stock or could adversely affect the rights and powers, including voting rights, of the holders of the common stock. In certain circumstances, such issuance could have the effect of decreasing the market price of the common stock;

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- The existence of a staggered board of directors in which there are three classes of directors serving staggered three-year terms, thus expanding the time required to change the composition of a majority of directors and perhaps discouraging someone from making an acquisition proposal for us;
- Our amended and restated bylaws requirement that shareholders provide advance notice when nominating director candidates to serve on our Board of Directors;
- The inability of shareholders to convene a shareholders meeting without the chairman of the board, the president or a majority of the board of directors first calling the meeting; and
- The application of Virginia law prohibiting us from entering into a business combination with the beneficial owner of 10% or more of our outstanding voting stock for a period of three years after the 10% or greater owner first reached that level of stock ownership, unless we meet certain criteria.

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

Other Risks Related to our Business

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

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

In particular, our efforts to comply with Section 404 of the Sarbanes-Oxley Act of 2002, to furnish a report by management on, among other things, the effectiveness and the related regulations regarding our required assessment of our internal controls over financial reporting and our external auditors audit of our internal control over financial reporting requires the commitment of significant financial and managerial resources. We consistently assess the adequacy of our internal controls over financial reporting, remediate any control deficiencies that may be identified, and validate through testing that our controls are functioning as documented. While we do not anticipate any material weaknesses, the inability of management and our independent auditor to provide us with an unqualified report as to the effectiveness of our internal controls over financial reporting for future year ends could result in adverse consequences to us, including, but not limited to, a loss of investor confidence in the reliability of our financial statements, which could cause the market price of our stock to decline. For example, in connection with our review of internal control over financial reporting as of December 31, 2012, we determined that we did not adequately implement certain controls over the

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administration, accounting and oversight of our 2000 Stock Incentive Plan, and we concluded that a material weakness in our internal control over financial reporting existed as of December 31, 2012. The existence of this or one or more other material weaknesses or significant deficiencies in our internal control over financial reporting could result in errors in our financial statements, and substantial costs and resources may be required to rectify any internal control deficiencies. Any material weaknesses may materially adversely affect our ability to report accurately our financial condition and results of operations in a timely and reliable manner. In addition, although we continually review and evaluate internal control systems to allow management to report on the sufficiency of our internal controls, we cannot assure you that we will not discover weaknesses in our internal control over financial reporting. Any such weakness or failure to remediate a material weakness could materially adversely affect our ability to comply with applicable financial reporting requirements and the requirements of our various agreements.

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

Additional Risks Related to this Offering and our Common Stock

We may allocate the net proceeds from this offering in ways that you and other shareholders may not approve.

We currently intend to use the net proceeds from this offering to fund further clinical development of ARIKAYCE for NTM patients and *Pseudomonas* in CF patients, to fund our efforts to obtain regulatory approvals and commercialize ARIKAYCE for NTM patients and *Pseudomonas* in CF patients, to invest in increased third-party manufacturing capacity in anticipation of potential commercial launch of ARIKAYCE in Europe and the United States and the balance to fund working capital, capital expenditures, general research and development, and other general corporate purposes, which may include the acquisition or in-license of additional compounds, product candidates, technology or businesses. This expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from clinical trials, as well as any strategic transactions that we may enter into with third parties for our product candidates, and any unforeseen cash needs. Because of the number and variability of factors that will determine our use of the proceeds from this offering, their ultimate use may vary substantially from their currently intended use. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering and could spend the proceeds in ways that do not necessarily improve our financial condition or operating results or enhance the value of our common stock. See Use of Proceeds.

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the book value of your shares.

The public offering price of our common stock is higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our net tangible book value per share after this offering. To the extent shares are issued under outstanding options or restricted stock units, you will incur further dilution. See Dilution for a more detailed description of the dilution to new investors in the offering.

A significant portion of our total outstanding shares may be sold into the market at any time, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Upon the completion of this offering, shares of our common stock beneficially owned by our executive officers and directors (other than Matthew Pauls, who has resigned effective August 22, 2014) will be subject to lock-up agreements with the underwriters that prohibit, subject to certain exceptions, the disposal or pledge of, or the hedging against, any of their common stock or securities convertible into or exchangeable for shares of common stock for a period of 90 days after the date of this prospectus supplement. However, all of the shares sold in this offering and the remaining shares of our common stock outstanding prior to this offering will not be subject to lock-up agreements with the underwriters and, except to the extent such shares are held by our affiliates, will be freely tradable without restriction. In addition, certain holders of our

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outstanding common stock have registration rights pursuant to which we may be required to register such shares for resale under the Securities Act of 1933. Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock.

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We may continue to need substantial additional funding. If we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the clinical development of and seek marketing approval for our product candidates, and scale up our operations in anticipation of product commercialization. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant additional commercialization expenses related to product sales, marketing, manufacturing and distribution. Accordingly, we may need to obtain substantial additional capital. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce or eliminate product development programs or commercialization efforts.

FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the other documents that are incorporated herein by reference contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, including statements regarding our strategy, operations, financial results and condition, prospects, plans and objectives, are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the results, plans, intentions or expectations indicated by our forward-looking statements, and you should not place undue reliance on our forward-looking statements. By their nature, forward-looking statements involve risks and uncertainties because they relate to events and depend on circumstances that may or may not occur in the future. These risks and uncertainties include, but are not limited to, those described in the Risk Factors section of this prospectus supplement and the accompanying prospectus. In addition, you should consider the information included under Risk Factors in our Annual Report on Form 10-K for the year ended December 31, 2013 and our subsequent quarterly reports on Form 10-Q, each of which is incorporated by reference in this prospectus supplement.

Unless required by law, we do not undertake and we specifically disclaim any obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of such statements or to reflect the occurrence of events, whether or not anticipated. We caution readers not to place undue reliance on any forward-looking statements, which speak only as of the date they are made.

USE OF PROCEEDS

We estimate that the net proceeds we will receive from this offering will be approximately \$94 million, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that the net proceeds from this offering will be approximately \$108 million.

We currently estimate that we will use the net proceeds from this offering as follows:

- to fund further clinical development of ARIKAYCE for NTM patients and *Pseudomonas* in CF patients;
- to fund our efforts to obtain regulatory approvals and commercialize ARIKAYCE for NTM patients and *Pseudomonas* in CF patients;
- to invest in increased third-party manufacturing capacity in anticipation of potential commercial launch of ARIKAYCE in Europe and the United States; and
- the balance to fund working capital, debt repayment, capital expenditures, general research and development, and other general corporate purposes, which may include the acquisition or in-license of additional compounds, product candidates, technology or businesses.

This expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development efforts, the status of and results from clinical trials, as well as any strategic transactions that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering. We have no current understandings, agreements or commitments for any material acquisitions or licenses of any compounds, product candidates, technology or businesses.

Pending our use of the net proceeds from this offering, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment grade, interest bearing instruments and U.S. government securities.

DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted immediately to the extent of the difference between the public offering price per share of our common stock and the pro forma net tangible book value per share of our common stock after this offering.

Our historical net tangible book value as of June 30, 2014 was \$53.3 million, or \$1.36 per share of our common stock, based upon 39,276,389 shares outstanding on June 30, 2014. Net tangible book value per share is equal to our total tangible assets, less our total liabilities, divided by the total number of shares outstanding as of June 30, 2014. After reflecting the sale of 8,900,000 shares of our common stock offered by us at the assumed public offering price of \$11.25 per share, less the estimated underwriting discounts and offering expenses, our as-adjusted net tangible book value would have been approximately \$147.2 million, or approximately \$3.06 per share of common stock based upon 48,176,389 shares outstanding. This represents an immediate increase in net tangible book value of \$1.70 per share to our existing shareholders and an immediate dilution in net tangible book value of \$8.19 per share to new investors. The following table illustrates this calculation on a per share basis:

Assumed public offering price per share		\$	11.25
Net tangible book value per share as of June 30, 2014	\$	1.36	
Increase in net tangible book value per share attributable to new investors	\$	1.70	
Pro forma net tangible book value per share after this offering	\$	3.06	
Dilution per share to new investors	\$	8.19	

The number of shares of our common stock to be outstanding after this offering excludes:

- 5,058,459 shares of our common stock issuable upon the exercise of stock options outstanding as of June 30, 2014 at a weighted average exercise price of \$10.42 per share; and
- 20,960 shares of our common stock issuable pursuant to unvested restricted stock units outstanding as of June 30, 2014 at a weighted average grant price of \$19.35.

UNDERWRITING

Subject to the terms and conditions set forth in the underwriting agreement, dated August 12, 2014, between us, and Leerink Partners LLC, as the representative of the underwriters named below and the sole book-running manager of this offering, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the respective number of shares of common stock shown opposite its name below:

Leerink Partners LLC	5,340,000
JMP Securities LLC	1,557,500
Total	8,900,000

Option to Purchase Additional Shares

We have granted to the underwriters an option, exercisable for 30 days from the date of this prospectus, to purchase, from time to time, in whole or in part, up to an aggregate of 1,335,000 shares of our common stock from us, at the public offering price set forth on the cover page of this prospectus, less underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to specified conditions, to purchase a number of additional shares proportionate to that underwriter's initial purchase commitment as indicated in the table above.

The underwriters have advised us that, following the completion of this offering, they currently intend to make a market in the common stock as permitted by applicable laws and regulations. However, the underwriters are not obligated to do so, and the underwriters may discontinue any market-making activities at any time without notice in their sole discretion. Accordingly, no assurance can be given as to the liquidity of the trading market for the common stock, that you will be able to sell any of the common stock held by you at a particular time or that the prices that you receive when you sell will be favorable.

The underwriters are offering the shares of common stock subject to their acceptance of the shares of common stock from us and subject to prior sale. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commission and Expenses

The underwriters have advised us that they initially propose to offer the shares of common stock to the public at the public offering price set forth on the cover page of this prospectus and to certain dealers, which may include the underwriters, at that price less a concession not in excess of \$0.405 per share of common stock. After the offering, the initial public offering price and concession may be reduced by the representative. No such reduction will change the amount of proceeds to be received by us as set forth on the cover page of this prospectus.

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The following table shows the public offering price, the underwriting discounts and commissions that we are to pay the underwriters and the proceeds, before expenses, to us in connection with this offering. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

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	Per Share	Without Option to Purchase Additional Shares	Total	With Option to Purchase Additional Shares
Public offering price	\$ 11.25	\$ 100,125,000	\$	115,143,750
Underwriting discounts and commissions paid by us	\$ 0.675	\$ 6,007,500	\$	6,908,625
Proceeds to us, before expenses	\$ 10.575	\$ 94,117,500	\$	108,235,125

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately \$250,000. We have agreed to reimburse the underwriters in an amount not to exceed \$25,000 for expenses related to the qualification of our common stock under state securities laws and clearing of this offering with the Financial Industry Regulatory Authority.

No Sales of Similar Securities

We and each of our executive officers (other than Matthew Pauls, our Chief Commercial Officer, who has resigned effective August 22, 2014), directors and certain shareholders have agreed that, subject to certain exceptions, without the prior written consent of Leerink Partners LLC, we and such executive officers and directors will not, during the period ending 90 days after the date of this prospectus supplement:

- offer, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, lend, or otherwise transfer or dispose of, directly or indirectly, any shares of common stock or securities convertible into or exercisable or exchangeable for common stock; or
- enter into any swap or other arrangement that transfers to another, in whole or in part, any of the economic consequences of ownership of the common stock;

whether any such transaction described above is to be settled by delivery of common stock or such other securities, in cash or otherwise.

In addition, during such 90-day restricted period, we have agreed not to file a registration statement (other than registration statements on Form S-8) with the Securities and Exchange Commission relating to the common stock.

The lock-up restrictions described in the immediately preceding paragraph do not apply to:

with respect to us:

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- the shares of our common stock to be sold in this offering;
- the issuance of shares of common stock upon the exercise of outstanding stock options or warrants or grants of stock options or other stock-based awards under our equity plans, or

with respect to our directors, executive officers and certain shareholders:

- transfers of shares of common stock or any security convertible into common stock as a bona fide gift or by will, other testamentary document or intestate succession;
- distributions of shares of common stock to limited partners, members, shareholders or wholly-owned subsidiaries of the director, officer or shareholder; transfers of shares of common stock or any security convertible into common stock pursuant to any order or settlement agreement not involving any public sale of shares of common stock or other securities and approved by any court of competent jurisdiction;

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- transfers of shares of common stock or any security convertible into common stock to any trust for the direct or indirect benefit of the director, officer or shareholder or the immediate family of such person;
- transfers of shares of common stock or any security convertible into common stock to any corporation, partnership, limited liability company or similar entity of which all of the beneficial ownership interests are held by the director, officer or shareholder or the immediate family of such person;
- the establishment of a new trading plan pursuant to Rule 10b5-1 under the Exchange Act providing for dispositions or sales of common stock, provided that such plan does not permit dispositions or sales of shares of common stock or any security convertible into common stock during the 90-day restricted period and no public announcement or filing under the Exchange Act regarding the establishment of such plan shall be voluntarily made during the 90-day restricted period;
- the exercise of options to purchase common stock outstanding as of the date hereof or granted under equity incentive plans in effect as of the date of this prospectus supplement, provided that the underlying common stock continues to be subject to the same restrictions described above;
- transfers of shares of common stock or any security convertible into common stock pursuant to a bona fide third party tender offer, merger, consolidation or other similar transaction made to holders of the common stock involving a change of control, provided that in the event that the tender offer, merger, consolidation or other such transaction is not completed, the directors, officers and certain shareholders remain subject to the restrictions described above;
- the repurchase or forfeiture of securities by us in connection with termination of the director or officer's employment; or
- the settlement of restricted stock, restricted stock units or options on a net basis or any other withholding of shares of common stock upon vesting and/or settlement of restricted stock, restricted stock units and/or options provided that (x) underlying common stock continues to be subject to the same restrictions described above and (y) the Company becomes the owner of the shares of common stock surrendered in the net exercise;

provided that in the case of any transfer or distribution described above in the first, second, third, fourth and fifth bullets, each donee, transferee or distributee agrees in writing to the same restrictions set forth above.

The directors, executive officers and certain shareholders have agreed that they shall provide Leerink Partners LLC two days' advance notice of any of the foregoing transfers, distributions, establishment of a plan, exercises, repurchases, forfeitures, settlements or withholdings, as applicable.

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In addition, our directors, executive officers and certain shareholders have agreed that, without the prior written consent of Leerink Partners LLC, they will not, during the 90-day restricted period, make any demand for or exercise any right with respect to, the registration of any shares of our common stock or any security convertible into or exercisable or exchangeable for our common stock.

There are no existing agreements between the underwriters and any of our shareholders who will execute a lock-up agreement providing consent to the sale of shares prior to the expiration of the lock-up period.

Stabilization

The underwriters have advised us that they, pursuant to Regulation M under the Securities Exchange Act of 1934, as amended, certain persons participating in the offering may engage in short sale transactions, stabilizing transactions, syndicate covering transactions or the imposition of penalty bids in connection with this offering. These activities may have the effect of stabilizing or maintaining the market price of the common stock at a level

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above that which might otherwise prevail in the open market. Establishing short sales positions may involve either covered short sales or naked short sales.

Covered short sales are sales made in an amount not greater than the underwriters' option to purchase additional shares of our common stock in this offering. The underwriters may close out any covered short position by either exercising their option to purchase additional shares of our common stock or purchasing shares of our common stock in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option to purchase additional shares.

Naked short sales are sales in excess of the option to purchase additional shares of our common stock. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the shares of our common stock in the open market after pricing that could adversely affect investors who purchase in this offering.

A stabilizing bid is a bid for the purchase of shares of common stock on behalf of the underwriters for the purpose of fixing or maintaining the price of the common stock. A syndicate covering transaction is the bid for or the purchase of shares of common stock on behalf of the underwriters to reduce a short position incurred by the underwriters in connection with the offering. Similar to other purchase transactions, the underwriter's purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. A penalty bid is an arrangement permitting the underwriters to reclaim the selling concession otherwise accruing to a syndicate member in connection with the offering if the common stock originally sold by such syndicate member are purchased in a syndicate covering transaction and therefore have not been effectively placed by such syndicate member.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. The underwriters are not obligated to engage in these activities and, if commenced, any of the activities may be discontinued at any time.

The underwriters may also engage in passive market making transactions in our common stock on The NASDAQ Global Select Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

A prospectus in electronic format may be made available by e-mail or on the web sites or through online services maintained by one or more of the underwriters or their affiliates. In those cases, prospective investors may view offering terms online and may be allowed to place orders online. The underwriters may agree with us to allocate a specific number of common stock for sale to online brokerage account holders. Any such allocation for online distributions will be made by the underwriters on the same basis as other allocations. Other than the prospectus in electronic format, the information on the underwriters' web sites and any information contained in any other web site maintained by any of the underwriters is not part of this prospectus, has not been approved and/or endorsed by us or the underwriters and should not be relied upon by investors.

Other Activities and Relationships

The underwriters and certain of their affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. The underwriters and certain of their affiliates have, from time to time, performed, and may in the future perform,

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various commercial and investment banking and financial advisory services for us and our affiliates, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and certain of its affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers, and such investment and securities activities may involve securities and/or instruments issued by us and our affiliates. If the underwriters or their respective affiliates have a lending relationship with us, they routinely hedge their credit exposure to us consistent with their customary risk management policies. The underwriters and their respective affiliates may hedge such exposure by entering into transactions which consist of either the purchase of credit default swaps or the creation of short positions in our securities or the securities of our affiliates, including potentially the common stock offered hereby. Any such short positions could adversely affect future trading prices of the common stock offered hereby. The underwriters and certain of their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such securities or instruments and may at any time hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

**MATERIAL UNITED STATES FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS
FOR NON-U.S. HOLDERS OF SHARES OF OUR COMMON STOCK**

The following is a summary of certain material United States federal income and estate tax considerations relating to the purchase, ownership, and disposition of shares of our common stock by a non-U.S. holder (as defined below) that acquires our common stock in this offering and holds it as a capital asset within the meaning of Section 1221 of the Internal Revenue Code of 1986, as amended (the Code) (generally, property held for investment). For purposes of this summary, a non-U.S. holder is a beneficial owner of our common stock that, for United States federal income tax purposes, is an individual, corporation, estate or trust other than:

- an individual who is a citizen or resident of the United States;
- a corporation, or any other organization taxable as a corporation for United States federal income tax purposes, that is created or organized under the laws of the United States, any state thereof, or the District of Columbia;
- an estate the income of which is subject to United States federal income taxation regardless of its source; or
- a trust if (1) a court within the United States is able to exercise primary supervision over the trust's administration and one or more United States persons (as defined in the Code) have the authority to control all substantial decisions of that trust, or (2) the trust has in effect a valid election under the applicable Treasury regulations to be treated as a United States person.

A modified definition of non-U.S. holder applies for United States federal estate tax purposes (as discussed below).

This summary is based upon the Code, Treasury regulations promulgated or proposed thereunder, judicial decisions, rulings, and administrative interpretations thereof, all as of the date hereof and all of which are subject to change, possibly with retroactive effect. The foregoing are subject to differing interpretations which could affect the tax consequences described herein. This summary does not purport to be a complete analysis of all the potential tax considerations relevant to non-U.S. holders of our common stock. In addition, this summary does not address all aspects of United States federal income and estate taxation that may be applicable to non-U.S. holders in light of their particular circumstances or status, nor does it address specific tax considerations that may be relevant to particular persons (including, for example, financial institutions, broker-dealers, insurance companies, partnerships or other pass-through entities, certain United States expatriates, tax-exempt organizations, pension plans, controlled foreign corporations, passive foreign investment companies, persons in special situations, such as those who have elected to mark securities to market or who hold shares of our common stock as part of a straddle, hedge or other integrated investment and holders subject to the alternative minimum tax or the Medicare tax on net investment income). In addition, except as explicitly addressed herein with respect to estate tax, this summary does not address certain estate tax considerations, any gift tax considerations, or any considerations under the tax laws of any state, local or non-United States jurisdiction.

If a partnership (including any entity or arrangement treated as a partnership for United States federal income tax purposes) owns our common stock, the tax treatment of a person treated as a partner in the partnership for United States federal income tax purposes generally will depend upon the status of the partner and the activities of the partnership. Partnerships and other entities that are treated as partnerships for United States

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federal income tax purposes and persons holding our common stock through a partnership or other entity treated as a partnership for United States federal income tax purposes should consult their tax advisors.

There can be no assurance that the Internal Revenue Service (IRS) will not challenge one or more of the tax consequences described herein, and we have not obtained, nor do we intend to obtain, a ruling from the IRS or an opinion of counsel with respect to the United States federal income or estate tax consequences to a non-U.S. holder of the purchase, ownership or disposition of our common stock.

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THIS SUMMARY IS FOR GENERAL INFORMATION ONLY AND IS NOT INTENDED TO BE LEGAL OR TAX ADVICE. YOU ARE URGED TO CONSULT YOUR TAX ADVISOR REGARDING THE UNITED STATES FEDERAL INCOME AND ESTATE TAXATION, STATE, LOCAL, AND NON-UNITED STATES TAXATION AND OTHER TAX CONSEQUENCES OF THE PURCHASE, OWNERSHIP, AND DISPOSITION OF OUR COMMON STOCK, INCLUDING THE CONSEQUENCES UNDER ANY APPLICABLE TAX TREATY.

Distributions with Respect to Shares of our Common Stock

As discussed above, we do not currently expect to pay dividends. In the event we do make a distribution of cash or property with respect to our common stock, any such distributions generally will constitute dividends for United States federal income tax purposes to the extent of our current or accumulated earnings and profits, as determined under United States federal income tax principles, and will be subject to withholding as described in the paragraph below. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder's investment, up to such holder's adjusted tax basis in shares of our common stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below in **Gain on Sale, Exchange or Other Taxable Disposition of Our Common Stock**. Any distribution described in this paragraph would also be subject to the discussion below in **Additional Withholding and Reporting Requirements**.

Any dividends paid to a non-U.S. holder with respect to shares of our common stock generally will be subject to withholding of United States federal tax at a 30% rate unless such non-U.S. holder provides us or our agent, as the case may be, with the appropriate and properly executed IRS Form W-8 prior to the payment of dividends (and periodically updated), such as:

- IRS Form W-8BEN or IRS Form W-8BEN-E, as applicable (or successor form) certifying, under penalties of perjury, that such non-U.S. holder is entitled to a reduction in withholding under an applicable income tax treaty, or
- IRS Form W-8ECI (or successor form) certifying, under penalties of perjury, that a dividend paid on our common stock is not subject to withholding tax because it is effectively connected with the conduct of a trade or business in the United States of the non-U.S. holder (and, if required by an applicable income tax treaty, is attributable to a permanent establishment or fixed base maintained in the U.S.), in which case such dividend generally will be subject to graduated United States federal income tax rates on a net income basis as described below.

The certification requirement described above also may require a non-U.S. holder that provides an IRS form or that claims treaty benefits to provide its United States taxpayer identification number.

Each prospective non-U.S. holder is urged to consult its own tax advisor about the specific methods for satisfying these requirements. A claim for exemption will not be valid if the person receiving the applicable form has actual knowledge or reason to know that the statements on the form are false.

If dividends are effectively connected with the conduct of a trade or business in the United States of a non-U.S. holder (and, if required by an applicable income tax treaty, are attributable to a permanent establishment or fixed base maintained by such non-U.S. holder in the United States), the non-U.S. holder, although exempt from the withholding tax described above (provided that the certifications described above are

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satisfied), will generally be subject to United States federal income tax on such dividends on a net income basis in the same manner as if it were a resident of the United States. In addition, if the non-U.S. holder is taxable as a corporation for United States federal income tax purposes, such holder may, under certain circumstances, be subject to an additional branch profits tax equal to 30% (unless reduced by an applicable income tax treaty) of its effectively connected earnings and profits for the taxable year.

If a non-U.S. holder is eligible for a reduced rate of United States federal withholding tax pursuant to an applicable income tax treaty, such holder may obtain a refund or credit of any amounts withheld in excess of that rate by timely filing an appropriate refund claim with the IRS.

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Gain on Sale, Exchange or Other Taxable Disposition of Shares of our Common Stock

Subject to the discussion below under **Additional Withholding and Reporting Requirements** and **Information Reporting and Backup Withholding**, a non-U.S. holder generally will not be subject to United States federal income tax or withholding tax on gain realized upon a sale, exchange or other taxable disposition of shares of our common stock (including a redemption, but only if the redemption would be treated as a sale or exchange rather than a distribution for United States federal income tax purposes) unless:

- (1) the gain is effectively connected with the conduct of a trade or business of the non-U.S. holder in the United States (and, if required by an applicable income tax treaty, the gain is attributable to a permanent establishment or fixed base maintained in the United States);
- (2) the non-U.S. holder is an individual who is present in the United States for 183 or more days in the taxable year of the disposition and meets certain other conditions; or
- (3) we are or have been a United States real property holding corporation (USRPHC) for United States federal income tax purposes at any time within the shorter of the five-year period preceding the disposition and the non-U.S. holder's holding period for our common stock (the relevant period).

If the first exception applies, the non-U.S. holder generally will be subject to United States federal income tax on a net income basis with respect to such gain in the same manner as if such holder were a resident of the United States. In addition, if the non-U.S. holder is a corporation for United States federal income tax purposes, such gains may, under certain circumstances, also be subject to an additional branch profits tax at a 30% rate (or at a lower rate under an applicable income tax treaty).

If the second exception applies, the non-U.S. holder generally will be subject to United States federal income tax at a rate of 30% (unless an applicable income tax treaty provides otherwise) on the amount by which such non-U.S. holder's capital gains allocable to United States sources exceed capital losses allocable to United States sources during the taxable year of the disposition.

With respect to the third exception above, although there can be no assurances, we believe we currently are not, and we do not anticipate becoming, a USRPHC for United States federal income tax purposes. Generally, a corporation is a USRPHC only if the fair market value of its United States real property interests (as defined in the Code) equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. Even if we are or become a USRPHC, a non-U.S. holder would not be subject to U.S. federal income tax on a sale, exchange or other taxable disposition of our common stock by reason of our status as a USRPHC so long as (i) our common stock continues to be regularly traded on an established securities market (within the meaning of Section 897(c)(3) of the Code) during the calendar year in which such disposition occurs and (ii) such non-U.S. holder does not own and is not deemed to own (directly, indirectly or constructively) more than 5% of our common stock at any time during the relevant period. If we are a USRPHC and the requirements of (i) or (ii) are not met, gain on the disposition of shares of our common stock generally will be taxed in the same manner as gain that is effectively connected with the conduct of a U.S. trade or business, except that the branch profits tax will not apply.

Additional Withholding and Reporting Requirements

Legislation commonly referred to as FATCA, as modified by Treasury regulations and subject to any official interpretations thereof, any applicable intergovernmental agreement between the United States and a non-U.S. government to implement these rules and improve international tax compliance, or any fiscal or regulatory legislation or rules adopted pursuant to any such agreement, generally imposes United States federal withholding at a rate of 30% on payments to certain non-U.S. entities (including financial intermediaries), including dividends on and the gross proceeds from dispositions of our common stock, unless various information reporting and due diligence requirements, which are different from and in addition to the certification requirements described elsewhere in this discussion, have been satisfied (generally relating to ownership by U.S. persons of interests in or accounts with those entities). The withholding rules applicable to payments of dividends on our common stock apply beginning July 1, 2014. The withholding rules will apply to gross proceeds from dispositions of our common stock beginning January 1, 2017. Although Treasury regulations implementing FATCA have been finalized, these rules remain unclear in several respects and are subject to material changes. An intergovernmental agreement between the United States and a foreign country where a holder or intermediary is located may modify the requirements in this paragraph. Prospective non-U.S.

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holders should consult their tax advisors regarding the possible implications of FATCA on their investment in our common stock.

Information Reporting and Backup Withholding

We or a financial intermediary must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions on our common stock paid to such holder and the tax withheld, if any, with respect to such distributions, regardless of whether withholding was required. A non-U.S. holder will generally be subject to backup withholding on dividends paid to such holder unless such holder furnishes a valid IRS Form W-8BEN or IRS Form W-8BEN-E, as applicable (or such other applicable form and documentation as required by the Code or the Treasury regulations) certifying under penalties of perjury that it is a non-U.S. holder (and the payor does not have actual knowledge or reason to know that such holder is a United States person as defined under the Code), or such holder otherwise establishes an exemption. Dividends paid to non-U.S. holders subject to the United States federal withholding tax, as described above in *Distributions with Respect to Shares of Our Common Stock*, generally will be exempt from U.S. backup withholding.

Information reporting and, depending on the circumstances, backup withholding will apply to the payment of the proceeds of a sale or other disposition of shares of our common stock by a non-U.S. holder effected by or through the United States office of any broker, United States or non-U.S., unless the holder certifies that it is not a United States person (as defined under the Code) and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-United States office of a broker. However, for information reporting purposes, dispositions effected through a non-United States office of a broker with substantial United States ownership or operations generally will be treated in a manner similar to dispositions effected through a United States office of a broker. Prospective investors should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of the information returns may be made available to the tax authorities in the country in which the non-U.S. holder resides or is incorporated under the provisions of an applicable treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a credit against a non-U.S. holder's United States federal income tax liability, if any, and may entitle such holder to a refund, provided that an appropriate claim is timely filed with the IRS.

Federal Estate Taxes

Shares of our common stock held (or treated as held) by an individual who is not a United States citizen or resident (as specifically determined for United States federal estate tax purposes) at the time of such individual's death generally will be included in the holder's gross estate for United States federal estate tax purposes, unless an applicable estate tax or other treaty provides otherwise, and, therefore, may be subject to United States federal estate tax.

LEGAL MATTERS

The validity of the common stock being offered by this prospectus will be passed upon for us by DLA Piper LLP (US), Short Hills, New Jersey. Ropes & Gray LLP, Boston, Massachusetts is counsel for the underwriters in connection with this offering.

EXPERTS

The financial statements and management's assessment of the effectiveness of internal control over financial reporting (which is included in Management's Report on Internal Control over Financial Reporting) incorporated herein by reference to the Annual Report on Form 10-K for the year ended December 31, 2013 have been so incorporated in reliance on the report of Ernst & Young LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to incorporate by reference into this prospectus supplement and the accompanying prospectus certain information we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference is considered to be part of this prospectus supplement and the accompanying prospectus, and information in documents that we file later with the SEC will automatically update and supersede information in this prospectus supplement and the accompanying prospectus. We incorporate by reference into this prospectus supplement and the accompanying prospectus the documents listed below and any future filings made by us with the SEC under Section 13(a), 13(c), 14 or 15(d) of the Exchange Act, except for information furnished under Items 2.02, 7.01 or 9.01 on Form 8-K or other information furnished to the SEC which is not deemed filed and not incorporated in this prospectus supplement and the accompanying prospectus, until the termination of the offering of securities described in this prospectus supplement. We hereby incorporate by reference the following documents:

- Annual Report on Form 10-K for the fiscal year ended December 31, 2013;
- Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2014 and June 30, 2014;
- Current Reports on Form 8-K filed on January 3, 2014, January 16, 2014, January 31, 2014, February 11, 2014, February 19, 2014, March 26, 2014, April 2, 2014, May 20, 2014, May 29, 2014; June 18, 2014, July 11, 2014 and August 4, 2014;
- Definitive Proxy Statement on Schedule 14A filed on April 17, 2014 (other than the portions thereof which are furnished and not filed);

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- Description of our common stock contained in our registration statement on Form 8-A dated June 1, 2000, as supplemented by the Description of Common Stock found on page 3 of the accompanying prospectus and including any amendments or reports filed for the purpose of updating such description; and
- All documents filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and before the last offering of common stock under this prospectus (excluding any portion of such documents which are furnished and not filed with the SEC).

You may access our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, Proxy Statement, and amendments to those documents, if any, filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act with the SEC free of charge at the SEC's website or our website as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC. The reference to our website does not constitute incorporation by reference of the information contained in our website. We do not consider information contained on, or that can be accessed through, our website to be part of this prospectus supplement.

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You may request a copy of our SEC filings at no cost, by telephoning or writing us at the following address:

Insmmed Incorporated
10 Finderne Avenue, Building 10
Bridgewater, New Jersey 08807
Attention: Christine Pellizzari, General Counsel and Corporate Secretary
(908) 977-9900

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PROSPECTUS

Common Stock

We may, from time to time, offer to sell common stock in amounts, at prices and on terms described in one or more supplements to this prospectus. You should read this prospectus and any supplement carefully before you invest.

This prospectus describes some of the general terms that may apply to an offering of our common stock. The specific terms and any other information relating to a specific offering will be set forth in a post-effective amendment to the registration statement of which this prospectus is a part or in a supplement to this prospectus or may be set forth in one or more documents incorporated by reference in this prospectus. The amendment or supplement, as applicable, may also add, update or change information contained in this prospectus with respect to that specific offering.

Our common stock may be offered and sold in the same offering or in separate offerings; to or through underwriters, dealers, and agents; or directly to purchasers; or through a combination of these methods. The names of any underwriter, dealer or agents involved in the sale of our common stock and their compensation will be described in an applicable prospectus supplement. See **Plan of Distribution** .

Our common stock is listed on The Nasdaq Global Select Market under the symbol **INSM** . On May 29, 2014, the last reported sale price for our common stock was \$13.26. You are encouraged to obtain current market quotations for shares of our common stock.

Our principal executive offices are located at 9 Deer Park Drive, Suite C, Monmouth Junction, New Jersey 08852, and our telephone number at that address is (732) 997-4600.

Investing in our common stock involves a high degree of risk. See **Risk Factors on page 2 of this prospectus.**

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is May 30, 2014.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or the SEC, using the shelf registration process as a well-known seasoned issuer, as defined in Rule 405 under the Securities Act of 1933, as amended, or the Securities Act. By using a shelf registration statement, we may offer and sell from time to time in one or more offerings the common stock described in this prospectus. No limit exists on the aggregate number of shares of common stock we may sell pursuant to the registration statement.

This prospectus provides you with a general description of our common stock. Each time we sell shares of our common stock, we will provide a prospectus supplement that will contain specific information about the terms of that offering. The prospectus supplement, or information incorporated by reference in this prospectus or any prospectus supplement that is of a more recent date, may also add, update or change information contained in this prospectus. To the extent that any statement that we make in a prospectus supplement is inconsistent with statements made in this prospectus, the statements made in this prospectus will be deemed modified or superseded by those made in the prospectus supplement. You should read both this prospectus and any applicable prospectus supplement, together with the additional information described below under the heading **Where You Can Find More Information**. This prospectus may not be used to consummate a sale of our common stock unless it is accompanied by a prospectus supplement. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to an offering of our common stock.

We have not authorized anyone to provide you with information other than the information contained or incorporated by reference in this prospectus and any related prospectus supplement, or in any free writing prospectus that we may authorize in connection with an offering of our shares of common stock. No one is making offers to sell or seeking offers to buy shares of our common stock in any jurisdiction where the offer or sale is not permitted. You should assume that the information contained in this prospectus and any prospectus supplement is accurate only as of the date on the front of this prospectus or the prospectus supplement, as applicable, and that any information we have incorporated by reference in this prospectus or any prospectus supplement is accurate only as of the date given in the document incorporated by reference, regardless of the time of delivery of this prospectus, any applicable prospectus supplement or any sale of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

References in this prospectus to Insmed , the Company , we , us and our refer to Insmed Incorporated, together with its consolidated subsidiaries.

ARIKACE® and IPLEX® are registered trademarks of Insmed Incorporated and Insmed™ and ARIKAYCE™ are trademarks of Insmed Incorporated. Our logos and trademarks are the property of Insmed. All other brand names or trademarks appearing in this prospectus are the property of their respective holders. Use or display by us of other parties' trademarks, trade dress, or products in this prospectus is not intended to, and does not, imply a relationship with, or endorsements or sponsorship of, us by the trademark or trade dress owners.

INSMED INCORPORATED

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.

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

In May 2014, we reported additional results from our phase 2 clinical trial. At the conclusion of the 84-day double blind phase of the trial, 78 of the 80 patients agreed to receive once-daily ARIKAYCE plus standard of care treatment for an additional 84 days. Data from 68 of these patients who completed the visits during the additional open label phase were available for analysis. These results collected from the open label phase show that 21 of these patients were culture negative for NTM at day 168. This data reflects 10 patients who were culture negative at day 84 as well as five additional patients from the ARIKAYCE arm and six additional patients who were on placebo, switching to ARIKAYCE during the open-label phase. The number of patients with negative cultures increased from the double blind phase of the trial in which 11 out of 44 patients treated with ARIKAYCE (added to standard of care treatment) demonstrated negative cultures by day 84 of the study as compared to three out of 45 patients treated with standard of care plus placebo.

Data analyses for certain additional secondary, tertiary and exploratory endpoints are ongoing. We also applied for Breakthrough Therapy Designation for ARIKAYCE in the US based upon the culture conversion results in our phase 2 clinical trial. ARIKAYCE has already received Orphan Drug, Qualified Infectious Disease Product (QIDP) and Fast Track designations from the US Food and Drug Administration (FDA) for the treatment of NTM lung infections and recently received Orphan Drug Designation from the European Medicines Agency (EMA).

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*). In this study, once-daily ARIKAYCE achieved its primary endpoint of non-inferiority when compared to twice-daily TOBI® (tobramycin inhaled solution) for relative change in forced expiratory volume in one second from baseline to the end of the study.

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 US, 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.

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

treatment of serious lung infections. Our principal executive offices are located at 9 Deer Park Drive, Suite C, Monmouth Junction, New Jersey 08852 and our phone number is (732) 997-4600. Our Internet address is www.insmed.com. The information on our web site is not incorporated by reference into this prospectus and should not be considered to be part of this prospectus.

RISK FACTORS

An investment in our common stock involves risks. Prior to making a decision about investing in our common stock, you should carefully consider the specific risks discussed under Risk Factors in any applicable prospectus supplement and in our filings with the Securities and Exchange Commission, or SEC, incorporated by reference in this prospectus, together with all of the other information contained in this prospectus and any applicable prospectus supplement or incorporated by reference in this prospectus. The risks and uncertainties described in any applicable prospectus supplement and in our SEC filings are not the only ones facing us. Additional risks and uncertainties not presently known to us, or that we currently see as immaterial, may also harm our business. If any of the risks or uncertainties described in any applicable prospectus supplement or our SEC filings or any such additional risks and uncertainties actually occur, our business, results of operations and financial condition could be materially and adversely affected. In that case, the trading price of our common stock could decline, and you might lose all or part of your investment.

NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains, and the documents incorporated by reference herein and any applicable prospectus supplement may contain, forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. These statements relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to statements about:

- the progress, timing, results or implications of clinical trials and other development activities involving our drug candidates;
- our plans and timing with respect to seeking regulatory approvals;
- the benefits to be derived from our drug candidates;
- the potential market opportunities for our drug candidates;
- the potential commercialization of any of our drug candidates that receive regulatory approval;

- our existing and potential future collaborations;
- our estimates of future payments, revenues and profitability; and
- our estimates regarding our capital requirements, future expenses and need for additional financing.

In some cases, you can identify forward-looking statements by terms such as *may* , *will* , *should* , *could* , *would* , *expects* , *plans* , *anticipates* , *believes* , *estimates* , *projects* , *predicts* , *potential* and similar expressions (including their use in the negative) intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss many of these risks in greater detail under the heading *Risk Factors* in our SEC filings, and may provide additional information in any applicable prospectus supplement. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement.

You should read this prospectus, the registration statement of which this prospectus is a part, the documents incorporated by reference herein, and any applicable prospectus supplement completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements.

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds from the sale of our common stock offered under this prospectus. Unless we indicate otherwise in the applicable prospectus supplement, we anticipate that any net proceeds will be used for working capital and general corporate purposes. We will set forth in the applicable prospectus supplement our intended use for the net proceeds received from the sale of any common stock sold pursuant to that prospectus supplement.

DESCRIPTION OF COMMON STOCK

The following is a description of the material terms and provisions of our common stock. It may not contain all the information that is important to you. You can access complete information by referring to our Articles of Incorporation, as amended (referred to herein as the Articles of Incorporation), and our Bylaws, as amended (referred to herein as the Bylaws), copies of which are filed as exhibits to the registration statement of which this prospectus forms a part.

General

Under our Articles of Incorporation, we have authority to issue 500,000,000 shares of common stock, par value \$0.01 per share. As of April 30, 2014, there were 39,272,501 shares of common stock issued and outstanding. All shares of common stock will, when issued pursuant to this prospectus, be duly authorized, fully paid and nonassessable. Accordingly, the full price for the outstanding shares of common stock will have been paid at issuance and any holder of our common stock will not be later required to pay us any additional money for such common stock.

Dividends

Subject to the prior rights of any series of preferred stock which may from time to time be outstanding, the holders of our common stock are entitled to receive such dividends, if any, as may be declared from time to time by our board of directors out of legally available funds. In the event we are liquidated, dissolved or our affairs are wound up, after we pay or make adequate provision for all of our known debts and liabilities, each holder of common stock will receive distributions pro rata out of assets that we can legally use to pay distributions, subject to any rights that are granted to the holders of any class or series of preferred stock. As of the date of this prospectus, we have not declared or paid any dividends on our shares of common stock.

Voting Rights

Holders of common stock will have the exclusive power to vote on all matters presented to our shareholders, including the election of directors, except as otherwise provided by Virginia law or as provided with respect to any other class or series of stock, as discussed in more detail below. Holders of common stock are entitled to one vote per share. There is no cumulative voting in the election of our directors, which means that, subject to any rights to elect directors that are granted to the holders of any class or series of preferred stock, a plurality of the votes cast at a meeting of shareholders at which a quorum is present is sufficient to elect a director.

Other Rights

Subject to the preferential rights of any other class or series of stock, all shares of common stock have equal dividend, distribution, liquidation and other rights, and have no preference, appraisal or exchange rights,

except for any appraisal rights provided by Virginia law. Furthermore, holders of common stock have no conversion, sinking fund or redemption rights, or preemptive rights to subscribe for any of our securities.

Transfer Agent

The transfer agent and registrar for our common stock is American Stock Transfer and Trust Company. Its address is 6201 15th Ave, Brooklyn, NY 11209.

Listing

Our common stock is listed on the Nasdaq Global Select Market under the symbol INSM.

PLAN OF DISTRIBUTION

We may sell the common stock to one or more underwriters for public offering and sale by them and may also sell the common stock to investors directly or through agents. We will name any underwriter or agent involved in the offer and sale of common stock in the applicable prospectus supplement. We have reserved the right to sell or exchange our common stock directly to investors on our own behalf in those jurisdictions where we are authorized to do so.

We may distribute the common stock from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

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We may also, from time to time, authorize dealers, acting as our agents, to offer and sell the common stock upon the terms and conditions set forth in the applicable prospectus supplement. We, or the purchasers of the common stock for whom the underwriters may act as agents, may compensate underwriters in the form of underwriting discounts or commissions, in connection with the sale of the common stock. Underwriters may sell the common stock to or through dealers, and those dealers may receive compensation in the form of discounts, concessions or commissions from the underwriters and/or commissions from the purchasers for whom they may act as agent. Unless otherwise indicated in the applicable prospectus supplement, an agent will be acting on a best efforts basis and a dealer will purchase the common stock as a principal, and may then resell the common stock at varying prices to be determined by the dealer.

We will describe in the applicable prospectus supplement any compensation we pay to underwriters or agents in connection with the offering of our common stock, and any discounts, concessions or commissions allowed by underwriters to participating dealers. Dealers and agents participating in the distribution of the common stock may be deemed to be underwriters, and any discounts and commissions received by them and any profit realized by them on resale of the common stock may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against certain civil liabilities, including liabilities under the Securities Act and to reimburse these persons for certain expenses. We may grant underwriters who participate in the distribution of the common stock we are offering under this prospectus an option to purchase additional shares in connection with the distribution.

To facilitate the offering of our common stock, certain persons participating in the offering may engage in transactions that stabilize, maintain, or otherwise affect the price of the common stock. This may include over-allotments or short sales of the common stock, which involve the sale by persons participating in the offering of more common stock than we sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their option to purchase additional shares, if any. In addition, these persons may stabilize or maintain the price of the common stock by bidding for or purchasing common stock in the open market or by imposing penalty bids, whereby selling

concessions allowed to dealers participating in the offering may be reclaimed if the common stock sold by them is repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the common stock at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

We may indemnify the underwriters, agents or dealers who participate in the distribution of our common stock against certain liabilities, including liabilities under the Securities Act. We may also contribute to payments that the underwriters, dealers or agents or any of their controlling persons may be required to make in respect of such liabilities. Certain underwriters, dealers or agents and their associates may engage in transactions with and perform services for us in the ordinary course of our business.

LEGAL MATTERS

The validity of the common stock being offered by this prospectus will be passed upon for us by DLA Piper LLP (US), Short Hills, New Jersey.

EXPERTS

The consolidated financial statements of Insmmed Incorporated appearing in Insmmed Incorporated's Annual Report on Form 10-K for the year ended December 31, 2013 and the effectiveness of Insmmed Incorporated's internal control over financial reporting as of December 31, 2013 have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their reports thereon, included therein, and incorporated herein by reference. Such consolidated financial statements and Insmmed Incorporated's management's assessment of the effectiveness of internal control over financial reporting as of December 31, 2013 are incorporated herein by reference in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We are a reporting company and we file annual, quarterly and current reports, proxy statements and other information with the SEC. We have filed with the SEC a registration statement under the Securities Act with respect to the common stock offered hereby. This prospectus, which constitutes a part of the registration statement, does not contain all of the information set forth in the registration statement or the exhibits which are part of the registration statement. For further information with respect to us and the common stock offered by this prospectus, we refer you to the registration statement and the exhibits filed as part of the registration statement. You may read and copy any document we file at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the Public Reference Room. Our SEC filings are also available to the public from the SEC's website at www.sec.gov. We maintain a website at www.insmed.com. The information contained in, or that can be accessed through, our website is not part of this prospectus.

The SEC allows us to incorporate by reference the information we file with it, which means that we can disclose important information to you by referring to those documents. The information incorporated by reference is an important part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We incorporate by reference the following documents we filed with the SEC pursuant to Section 13 of the Exchange Act:

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- Annual Report on Form 10-K for the fiscal year ended December 31, 2013;
- Quarterly Report on Form 10-Q for the quarter ended March 31, 2014;
- Current Reports on Form 8-K filed on January 3, 2014, January 16, 2014, January 31, 2014, February 11, 2014, February 19, 2014, March 26, 2014, April 2, 2014, May 20, 2014 and May 29, 2014;
- Definitive Proxy Statement on Schedule 14A filed on April 17, 2014 (other than the portions thereof which are furnished and not filed);

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- Description of our common stock contained in our registration statement on Form 8-A dated June 1, 2000; and
- All documents filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus and before the last offering of common stock under this prospectus (excluding any portion of such documents which are furnished and not filed with the SEC).

You may access our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, Proxy Statement, and amendments to those documents, if any, filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act with the SEC free of charge at the SEC's website or our website as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC. The reference to our website does not constitute incorporation by reference of the information contained in our website. We do not consider information contained on, or that can be accessed through, our website to be part of this prospectus or the related registration statement.

You may request a copy of our SEC filings at no cost, by telephoning or writing us at the following address:

Insmed Incorporated
9 Deer Park Drive, Suite C
Monmouth Junction, New Jersey 08852
Attention: Christine Pellizzari, General Counsel and Corporate Secretary
(732) 997-4600

8,900,000

Shares

Sole Book-Running Manager

Leerink Partners

Lead Managers

Piper Jaffray

JMP Securities

Co-Manager

H.C. Wainwright & Co., LLC