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Form 10-K
February 22, 2019
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2018

OR

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

For the transition period from _____ to _____

Commission File Number 0-30739

INSMED INCORPORATED

(Exact name of registrant as specified in its charter)

Virginia	**54-1972729**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. employer identification no.)**
10 Finderne Avenue, Building 10 **Bridgewater, New Jersey 08807**	**(908) 977-9900**
(Address of principal executive offices)	**(Registrant's telephone number including area code)**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Name of each exchange on which registered
Common Stock, par value $0.01 per share	**Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes [ü] No [ ]

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes [ ] No [ü]

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes [ü] No [ ]

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes [ü] No [ ]

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. [ ]

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company (See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act). Large accelerated filer [ü] Accelerated filer [ ] Non-accelerated filer [ ] Smaller reporting company [ ] Emerging growth company [ ]

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act [ ]

Indicate by check mark whether the registrant is a Shell Company (as defined in Rule 12b-2 of the Exchange Act). Yes [ ] No [ü]

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant on June 30, 2018, was $1,803 million (based on the closing price for shares of the registrant's common stock as reported on the Nasdaq Global Select Market on that date). In determining this figure, the registrant has assumed solely for this purpose that all of its directors, executive officers, persons beneficially owning 10% or more of the registrant's outstanding common stock and certain other stockholders of the registrant may be considered to be affiliates. This assumption shall not be deemed conclusive as to affiliate status for this or any other purpose.

On February 15, 2019, there were 77,538,562 shares of the registrant's common stock, $0.01 par value, outstanding.

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DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for its 2019 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission no later than April 30, 2019 and to be delivered to shareholders in connection with the 2019 Annual Meeting of Shareholders, are herein incorporated by reference in Part III of this Form 10-K.

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INSMED INCORPORATED
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Unless the context otherwise indicates, references in this Form 10-K to “Insmed Incorporated” refers to Insmed Incorporated, a Virginia corporation, and “Company,” “Insmed,” “we,” “us” and “our” refer to Insmed Incorporated together with its consolidated subsidiaries. INSMED, CONVERT and ARIKAYCE are trademarks of Insmed Incorporated. This Form 10-K also contains trademarks of third parties. Each trademark of another company appearing in this Form 10-K is the property of its owner.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

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

Forward-looking statements are based on our current expectations and beliefs, and involve known and unknown risks, uncertainties and other factors, which may cause our actual results, performance and achievements and the timing of certain events to differ materially from the results, performance, achievements or timing discussed, projected, anticipated or indicated in any forward-looking statements. Such risks, uncertainties and other factors include, among others, the following:

- *failure to successfully commercialize or maintain US approval for ARIKAYCE® (amikacin liposome inhalation suspension), our only approved product;*
- *uncertainties in the degree of market acceptance of ARIKAYCE by physicians, patients, third-party payors and others in the health-care community;*
- *our inability to obtain full approval of ARIKAYCE from the US Food and Drug Administration (FDA), including the risk that we will not successfully complete the confirmatory post-marketing study required for full approval;*
- *inability of us, PARI Pharma GmbH (PARI) or our third-party manufacturers to comply with regulatory requirements related to ARIKAYCE or the Lamira Nebulizer System (Lamira);*
- *our inability to obtain adequate reimbursement from government or third-party payors for ARIKAYCE or acceptable prices for ARIKAYCE;*
- *development of unexpected safety or efficacy concerns related to ARIKAYCE;*
- *inaccuracies in our estimates of the size of the potential markets for ARIKAYCE or in data we have used to identify physicians;*
- *our inability to create an effective direct sales and marketing infrastructure or to partner with third parties that offer such an infrastructure for distribution of ARIKAYCE;*
- *failure to obtain regulatory approval to expand ARIKAYCE's indication to a broader patient population;*
- *failure to successfully conduct future clinical trials for ARIKAYCE and our product candidates, including due to our limited experience in conducting preclinical development activities and clinical trials necessary for regulatory approval and our inability to enroll or retain sufficient patients to conduct and complete the trials or generate data necessary for regulatory approval;*
- *risks that our clinical studies will be delayed or that serious side effects will be identified during drug development;*
- *failure to obtain regulatory approvals for ARIKAYCE outside the US or for our product candidates in the US, Europe, Japan or other markets;*
- *failure of third parties on which we are dependent to manufacture sufficient quantities of ARIKAYCE or our product candidates for commercial or clinical needs, to conduct our clinical trials, or to comply with our agreements or laws and regulations that impact our business;*
- *our inability to attract and retain key personnel or to effectively manage our growth;*
- *our inability to adapt to our highly competitive and changing environment;*
- *our inability to adequately protect our intellectual property rights or prevent disclosure of our trade secrets and other proprietary information and costs associated with litigation or other proceedings related to such matters;*

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- *restrictions or other obligations imposed on us by agreements related to ARIKAYCE or our product candidates, including our license agreements with PARI and AstraZeneca AB (AstraZeneca), and failure to comply with our obligations under such agreements;*
- *the cost and potential reputational damage resulting from litigation to which we are or may become a party, including product liability claims;*
- *limited experience operating internationally;*
- *changes in laws and regulations applicable to our business and failure to comply with such laws and regulations; and*
- *inability to repay our existing indebtedness and uncertainties with respect to our ability to access future capital.*

We caution readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made. Any forward-looking statement is based on information current as of the date of this Annual Report on 10-K and speaks only as of the date on which such statement is made. Actual events or results may differ materially from the results, plans, intentions or expectations anticipated in these forward-looking statements as a result of a variety of factors, many of which are beyond our control. More information on factors that could cause actual results to differ materially from those anticipated is included from time to time in our reports filed with the Securities and Exchange Commission (SEC), including, but not limited to, those described in the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in this Annual Report on Form 10-K. We disclaim any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

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PART I

ITEM 1. BUSINESS

Business Overview

We are a global biopharmaceutical company on a mission to transform the lives of patients with serious and rare diseases. Our first commercial product, ARIKAYCE (amikacin liposome inhalation suspension), received accelerated approval in the United States (US) on September 28, 2018 for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options in a refractory setting, as defined by patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. MAC lung disease is a rare and often chronic infection that can cause irreversible lung damage and can be fatal. Our clinical-stage pipeline includes INS1007 and INS1009. INS1007 is a novel oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1) with therapeutic potential in non-cystic fibrosis (non-CF) bronchiectasis and other inflammatory diseases. INS1009 is an inhaled formulation of a treprostinil prodrug that may offer a differentiated product profile for rare pulmonary disorders, including pulmonary arterial hypertension (PAH).

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

Principal Product/Product Candidate	Status	Next Expected Milestones
ARIKAYCE for MAC lung disease	• We continue to focus on having a successful commercial launch of ARIKAYCE in the US for appropriate patients. We began commercial shipments of ARIKAYCE in October 2018. • In September 2018, the FDA granted accelerated approval of ARIKAYCE for the treatment of refractory MAC lung disease as part of a combination antibacterial drug regimen for adult patients who have limited or no alternative treatment options. • The FDA has designated ARIKAYCE as an orphan drug and a qualified infectious disease product (QIDP) for nontuberculous mycobacterial (NTM) lung disease, and the European Commission has granted an orphan designation for ARIKAYCE for the treatment of NTM lung disease.	• We intend to submit regulatory filings for ARIKAYCE in Europe in mid-2019 and Japan in the first half of 2020. If approved, we expect ARIKAYCE would be the first inhaled therapy specifically indicated for the treatment of MAC lung disease in Europe and Japan. • If approved, we plan to commercialize ARIKAYCE in certain countries in Europe, Japan and certain other countries. • We intend to collaborate with the FDA on, and invest in, the post-approval confirmatory clinical trial required by the FDA to support full approval and intend to complete the design and protocol of the confirmatory study during the first half of 2019. We also intend to collaborate with the FDA on lifecycle management programs.
INS1007 (oral reversible inhibitor of DPP1) for non-CF bronchiectasis and other rare diseases	• We are enrolling patients in the WILLOW study, a global phase 2, randomized, double-blind, placebo-controlled, parallel-group, multi-center clinical study to assess the efficacy, safety and tolerability, and pharmacokinetics of INS1007 administered once daily for 24 weeks in subjects with non-CF bronchiectasis.	• We expect to complete enrollment in the WILLOW clinical study of INS1007 in mid-2019. • We are exploring the potential of INS1007 in various neutrophil-driven inflammatory conditions.
INS1009 (inhaled formulation of a treprostinil prodrug) for rare pulmonary disorders	• The results of our phase 1 study of INS1009 were presented at the European Respiratory Society international congress in September 2016.	• We believe INS1009 may offer a differentiated product profile for rare pulmonary disorders, including PAH, and we are currently evaluating our options to advance its development including exploring its use as an inhaled dry powder formulation.

Our earlier-stage pipeline includes preclinical compounds that we are evaluating in multiple rare diseases of unmet medical need, including gram positive pulmonary infections in CF, NTM lung disease and refractory localized infections involving biofilm. To complement our internal research and development, we actively evaluate in-licensing and acquisition opportunities for a broad range of rare diseases.

Our Strategy

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Our strategy focuses on the needs of patients with rare diseases. We secured US regulatory approval of ARIKAYCE for the treatment of refractory MAC lung disease in patients with limited or no alternative treatment options. We are currently primarily focused on the US commercial launch of ARIKAYCE. We are not aware of any other approved inhaled therapies specifically indicated to treat MAC lung disease in North America, Europe or Japan. We believe that ARIKAYCE has the potential to prove beneficial in other patients with MAC, as well as in other infections. We are also advancing earlier-stage programs in other rare pulmonary disorders.

Our current priorities are as follows:

- Continue our efforts to ensure a successful US launch of ARIKAYCE;
- Complete the design and protocol of the confirmatory clinical trial during the first half of 2019 required for the full US approval of ARIKAYCE by the FDA in patients with MAC;
- Accelerate our global expansion efforts to support potential regulatory filings for ARIKAYCE in Europe in mid-2019 and Japan in the first half of 2020;
- Advance our pipeline, which is intended to bring additional therapies to market for patients with serious and rare diseases, including completing enrollment in the WILLOW study, our six-month Phase 2 trial of INS1007 in patients with non-cystic fibrosis bronchiectasis, in mid-2019.
- Ensure our product supply chain will support the global commercialization and potential future lifecycle management programs of ARIKAYCE;
- Develop the core value dossier to support the reimbursement for ARIKAYCE in the US, Europe and Japan;
- Obtain determinations of coverage and reimbursement in the US for ARIKAYCE from governmental and other third-party payors;
- Support further research and lifecycle management strategies for ARIKAYCE in the US, including exploring the potential use of ARIKAYCE as part of a front-line, multi-drug regimen and as a maintenance therapy to prevent recurrence (defined as true relapse or reinfection) of MAC lung disease;
- Explore INS1009 for use as an inhaled dry powder formulation and generating preclinical findings from our earlier-stage programs; and
- Expand our rare disease pipeline through corporate development.

ARIKAYCE for Patients with MAC Lung Disease

ARIKAYCE is our first approved product. ARIKAYCE received accelerated approval in the US on September 28, 2018 for the treatment of refractory MAC lung disease as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options. MAC lung disease is a rare and often chronic infection that can cause irreversible lung damage and can be fatal. Amikacin solution for parenteral administration is an established drug that has activity against a variety of NTM; however, its use is limited by the need to administer it intravenously and by toxicity to hearing, balance, and kidney function (Peloquin et al., 2004). Unlike amikacin solution for intravenous administration, our proprietary Pulmovance™ technology uses charge-neutral liposomes to deliver amikacin directly to the lungs where liposomal amikacin is taken up by the lung macrophages where the MAC infection resides. This technology also prolongs the release of amikacin in the lungs, while minimizing systemic exposure, thereby offering the potential for decreased systemic toxicities. ARIKAYCE's ability to deliver high levels of amikacin directly to the lung and sites of MAC infection via the use of our Pulmovance technology, distinguishes it from intravenous amikacin. ARIKAYCE is administered once-daily, using Lamira®, an inhalation device developed and manufactured by PARI. Lamira is a portable nebulizer that enables aerosolization of liquid medications via a vibrating, perforated membrane, and was designed specifically for ARIKAYCE delivery.

The FDA has designated ARIKAYCE as an orphan drug and a QIDP for NTM lung disease. Orphan designated drugs are eligible for seven years of exclusivity for the orphan indication. QIDP designation features an additional five years of exclusivity for the designated indication. The FDA granted a total of 12 years of exclusivity in the indication for which ARIKAYCE was approved.

US Marketing Approval

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In March 2018, we submitted a new drug application (NDA) for ARIKAYCE to the FDA pursuant to Section 506(c) of the Federal Food Drug and Cosmetic Act and 21 C.F.R. Part 314 Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) (Subpart H). Accelerated approval allows drugs that (i) are being developed to treat a serious or life-threatening disease or condition and (ii) provide a meaningful therapeutic benefit over existing treatments to be approved substantially based on an intermediate endpoint or a surrogate endpoint that is reasonably likely to predict clinical benefit, rather than a clinical endpoint such as survival or irreversible morbidity. The FDA granted our request for a priority review and set a Prescription Drug Use Fee Act (PDUFA) action date of September 28, 2018. On August 7, 2018, the FDA Antimicrobial Drugs Advisory Committee voted in favor of the safety and effectiveness of ARIKAYCE as part of a combination antibacterial drug regimen for adults with MAC lung disease who have limited or no treatment options. The committee also voted in favor of the surrogate endpoint of sputum culture conversion used in the Phase 3 CONVERT study being reasonably likely to predict clinical benefit. In a separate vote, the committee voted that there was insufficient existing evidence of the safety and effectiveness of ARIKAYCE in the broader population of adult patients with MAC lung disease. On September 28, 2018, the FDA granted approval for ARIKAYCE under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) for the treatment of refractory MAC lung disease as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options via the accelerated approval pathway. LPAD, which was enacted as part of the 21st Century Cures Act, serves to advance the development of new antibacterial drugs to treat serious or life-threatening infections in limited populations of patients with unmet needs. As required for drugs approved under the LPAD pathway, labeling for ARIKAYCE includes certain statements to convey that the drug has been shown to be safe and effective only for use in a limited population.

As a condition of accelerated approval, we must conduct a post-approval confirmatory clinical trial. The required confirmatory trial, which is currently under discussion with FDA, is proposed to be a randomized, double-blind, placebo-controlled clinical trial to assess and describe the clinical benefit of ARIKAYCE in patients with MAC lung disease. The trial will evaluate the effect of ARIKAYCE on a clinically meaningful endpoint, as compared to an appropriate control, in the intended patient population of patients with MAC lung disease. Pursuant to the timetable agreed upon with the FDA, the study protocol is expected to be finalized during the first half of 2019, with trial results to be reported by 2024. Continued approval of ARIKAYCE will be contingent upon verification and description of clinical benefit in this study.

Clinical Trials

Accelerated approval of ARIKAYCE was supported by preliminary data from our CONVERT study, a global Phase 3 study evaluating the safety and efficacy of ARIKAYCE in adult patients with refractory MAC lung disease, using achievement of sputum culture conversion (defined as three consecutive negative monthly sputum cultures) by Month 6 as the primary endpoint. Patients who achieved sputum culture conversion by Month 6 continued in the CONVERT study for an additional 12 months of treatment following the first monthly negative sputum culture in order to assess the durability of culture conversion, as defined by patients that have completed treatment and continued in the CONVERT study off all therapy for three months. We previously reported interim durability data as of December 2017, in which 60.9% of patients (28/46) who had achieved the primary endpoint at Month 6 on ARIKAYCE plus guidelines-based therapy (GBT) remained culture negative three months off all therapy, compared to 0.0% of patients (0/7) who had achieved the primary endpoint at Month 6 on GBT only. Final durability data for patients three months off all therapy were consistent with these interim data, and safety data for these patients were consistent with safety data previously reported for patients by Month 6 of the CONVERT study. The CONVERT study is ongoing.

Patients who did not culture convert by Month 6 may have been eligible to enroll in our 312 study, an open-label extension study for these non-converting patients who completed six months of treatment in the CONVERT study. The primary objective of the 312 study was to evaluate the long-term safety and tolerability of ARIKAYCE in

combination with a standard multi-drug regimen. The secondary objectives of the 312 study included evaluating the proportion of subjects achieving culture conversion (defined in the same way as the CONVERT study) by Month 6 and the proportion of subjects achieving culture conversion by Month 12, which was the end of treatment. We previously reported interim data as of December 2017 for patients in the 312 study, with 28.4% of patients who received GBT only in the CONVERT study (19/67) and 12.3% of patients who had received ARIKAYCE plus GBT in the CONVERT study (7/57) achieving culture conversion by Month 6 of the 312 study. The 312 study has concluded. Final efficacy data regarding culture conversion were consistent with these interim data. We are continuing to analyze the safety and efficacy data from the 312 study, but we have not identified any new safety signals.

Further Research and Lifecycle Management

We are currently exploring and supporting research and lifecycle management programs for ARIKAYCE in the US beyond treatment of refractory MAC lung disease as part of a combination antibacterial regimen for adult patients who have limited or no treatment options. Specifically, we are evaluating future study designs focusing on the MAC lung disease

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treatment pathway, including front-line treatment and maintenance to prevent recurrence (defined as true relapse or reinfection) of MAC lung disease. As noted above, we plan to conduct our required confirmatory trial to assess and describe the clinical benefit of ARIKAYCE in patients with MAC lung disease.

If the data from the CONVERT study are sufficient to support our marketing authorization applications (MAAs) in Europe and Japan and those regulatory bodies approve ARIKAYCE, lifecycle management studies could potentially enable us to reach more patients worldwide. In addition, the use of ARIKAYCE to treat infections caused by non-MAC NTM species, such as *M. abscessus,* is being evaluated. These initiatives include investigator-initiated studies, which are clinical studies initiated and sponsored by physicians or research institutions with funding from us, and may also include new clinical studies sponsored by us.

Market Opportunity for ARIKAYCE in MAC Lung Disease

NTM lung disease is associated with increased rates of morbidity and mortality, and MAC is the predominant pathogenic species in NTM lung disease in the US, Europe and Japan. The prevalence of NTM lung disease has increased over the past two decades, and we believe it is an emerging public health concern worldwide. Based on an analysis conducted in 2017 using information from external sources, including market research funded by us and third parties, and internal analyses and calculations, we estimated potential patient populations for 2018 in the US, the EU5 (comprised of France, Germany, Italy, Spain and the United Kingdom) and Japan as follows:

Potential Market	Estimated Number of Patients with Diagnosed NTM Lung Disease	Estimated Number of Patients Treated for MAC Lung Disease	Estimated Number of MAC lung disease Patients Refractory to Treatment**
United States	75,000-105,000	40,000-50,000	10,000-15,000
EU5	14,000	4,400	1,400
Japan	125,000-145,000	60,000-70,000	15,000-18,000

*** ARIKAYCE received accelerated approval for this population in the US in September 2018.*

We are not aware of any other approved inhaled therapies specifically indicated for NTM lung disease in North America, Europe or Japan. Current guideline-based approaches for NTM lung disease, including those from the American Thoracic Society and Infectious Diseases Society of America, involve multi-drug regimens not approved for the treatment of NTM lung disease and treatment that could last two years or more. Based on a burden of illness study that we conducted in the US with a major medical benefits provider, we previously concluded that patients with NTM lung disease are costly to healthcare plans, while a recent claims-based study in the US has shown that patients with NTM lung disease have higher resource utilization and costs than their age and gender-matched controls. Accordingly, we believe that a significant market opportunity for ARIKAYCE in NTM lung disease exists in the US and internationally.

We are currently exploring the MAC lung disease market opportunity for ARIKAYCE in Japan and Europe. The CONVERT study included a comprehensive pharmacokinetic sub-study in Japanese subjects in lieu of a separate local pharmacokinetic study in Japan, as agreed with the Pharmaceuticals and Medical Devices Agency (PMDA). If the data from the CONVERT study are sufficient to support our MAAs, we expect to submit regulatory filings in Europe in mid-2019 and Japan in the first half of 2020. We established a Japanese subsidiary and, in 2018, began hiring local employees, including a general manager, to manage our regulatory and pre-commercial activities.

Product Pipeline

INS1007

INS1007 is a small molecule, oral, reversible inhibitor of DPP1, which we licensed from AstraZeneca in October 2016. DPP1 is an enzyme responsible for activating neutrophil serine proteases in neutrophils when they are formed in

the bone marrow. Neutrophils are the most common type of white blood cell and play an essential role in pathogen destruction and inflammatory mediation. Neutrophils contain the neutrophil serine proteases (including neutrophil elastase, proteinase 3, and cathepsin G) that have been implicated in a variety of inflammatory diseases. In chronic inflammatory lung diseases, neutrophils accumulate in the airways and release active neutrophil serine proteases in excess that cause lung destruction and inflammation. INS1007 may decrease the damaging effects of inflammatory diseases, such as non-CF bronchiectasis, by inhibiting DPP1 and its activation of neutrophil serine proteases. Non-CF bronchiectasis is a progressive pulmonary disorder in which the bronchi become permanently dilated due to chronic inflammation and infection. Currently, there is no cure, and we are not aware of any FDA-approved therapies specifically indicated for non-CF bronchiectasis.

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The WILLOW Study

The WILLOW study is a global phase 2, randomized, double-blind, placebo-controlled, parallel group, multi-center clinical study to assess the efficacy, safety and tolerability, and pharmacokinetics of INS1007 administered once daily for 24 weeks in subjects with non-CF bronchiectasis. We commenced enrollment in the WILLOW study in December 2017, which we expect to complete in mid-2019. In addition, we are exploring the potential of INS1007 in various neutrophil-driven inflammatory conditions.

INS1009

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

Corporate Development

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

Manufacturing

We do not have any in-house manufacturing capability other than for small-scale pre-clinical development programs, and depend completely on a small number of third-party manufacturers and suppliers for the manufacture of our product candidates for use in clinical trials. We plan to rely on third-party manufacturers and suppliers for the commercial manufacture and supply of any product candidates that we commercialize. ARIKAYCE is manufactured currently by Therapure Biopharma Inc. (Therapure) in Canada at a 200 kilogram (kg) scale and by Ajinimoto Althea, Inc. (Althea) in the US at a 50 kg scale. For additional information about our agreements with Therapure and Althea, see *License and Other Agreements—ARIKAYCE-Related Agreements*.

In October 2017, we entered into certain agreements with Patheon UK Limited (Patheon) related to increasing our long-term production capacity for ARIKAYCE commercial inventory. The agreements provide for Patheon to manufacture and supply ARIKAYCE for our long-term anticipated commercial needs. Under these agreements, we are required to deliver to Patheon the required raw materials, including active pharmaceutical ingredients, and certain fixed assets needed to manufacture ARIKAYCE. The investment in the long-term production capacity build-out, including these agreements, and related agreements or purchase orders with third parties for raw materials and fixed assets, is estimated to be approximately $60 million. In addition, we have a commercialization agreement with PARI, the manufacturer of our drug delivery nebulizer for ARIKAYCE, to address our commercial supply needs (Commercialization Agreement).

In May 2017, we entered into a commercial supply agreement with AstraZeneca related to certain short-term production needs for INS1007. We expect our future requirements for INS1007, beyond phase 2, will be manufactured by a contract manufacturing organization (CMO).

We currently produce INS1009 and plan to utilize third parties to manufacture INS1009 at a larger scale and to manufacture the delivery device.

Intellectual Property

We own or license rights to more than 350 issued patents and pending patent applications in the US and in foreign countries, including more than 175 issued patents and pending patent applications related to ARIKAYCE. Our success depends in large part on our ability to maintain proprietary protection surrounding our product candidates, technology and know-how; to operate without infringing the proprietary rights of others; and to prevent others from infringing our proprietary rights. We actively seek patent protection by filing patent applications, including on inventions that are important to the development of our business in the US, Europe, Japan, Canada, and selected other foreign markets that we consider key for our product candidates. These international markets generally include Australia, China, India, Israel, and Mexico.

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

We monitor for activities that may infringe our proprietary rights, as well as the progression of third-party patent applications that may have the potential to create blocks to our products or otherwise interfere with the development of our business. We are aware, for example, of US patents, and corresponding international counterparts, owned by third parties that contain claims related to treating lung infections using inhaled antibiotics. If any of these patents were to be asserted against us, we do not believe that our proposed products would be found to infringe any valid claim of these patents.

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

ARIKAYCE Patents and Trade Secrets

Of the patents and applications related to ARIKAYCE, there are nine issued US patents that cover the ARIKAYCE composition and its use in treating NTM. These patents are listed in the FDA Orange Book. These patents and their expiration dates are as follows:

- US Patent No. 7,718,189 (expires June 6, 2025)
- US Patent No. 8,226,975 (expires August 15, 2028)
- US Patent No. 8,632,804 (expires December 5, 2026)
- US Patent No. 8,802,137 (expires April 8, 2024)
- US Patent No. 8,679,532 (expires December 5, 2026)
- US Patent No. 8,642,075 (expires December 5, 2026)
- US Patent No. 9,566,234 (expires January 18, 2034)
- US Patent No. 9,827,317 (expires April 8, 2024)
- US Patent No. 9,895,385 (expires May 15, 2035)

In addition, we own six pending US patent applications that cover the ARIKAYCE composition and/or its use in treating NTM. We also own a pending US application that covers methods for making ARIKAYCE. These patent applications, if issued as patents in their current form, may be eligible for listing in the FDA Orange Book for ARIKAYCE.

Four patents have been granted by the European Patent Office (EPO) (European Patent Nos. 1581236, 1909759, 1962805 and 2363114) that relate to ARIKAYCE and its use in treating NTM. In addition, we have five applications pending before the EPO that relate to ARIKAYCE and its use in treating NTM lung disease. We also have a pending European application that describes certain methods of making ARIKAYCE. More than 40 patents have also been issued in other major foreign markets, e.g., Japan, China, Korea, Australia, and India, that relate to ARIKAYCE and/or methods of using ARIKAYCE for treating various pulmonary disorders, including NTM lung disease. More than 60 foreign patent applications are pending that relate to the ARIKAYCE composition and/or its use in treating various pulmonary disorders, including NTM lung disease. We anticipate that in the US, we will have potential patent coverage for ARIKAYCE and its use in treating NTM lung disease, through May 15, 2035.

European Patent No. 2363114 was opposed by Generics (UK) Ltd, a wholly-owned subsidiary of Mylan NV, and was revoked in November 2017. We have appealed that decision, and the patent remains enforceable during the appeal.

European Patent No. 1909759 (the '759 patent), owned by us, was previously opposed by Generics (UK) Ltd. A hearing was held on October 19, 2015, during which we submitted amended claims. The European Patent Office Opposition Division (EPOOD) maintained the patent as amended and Generics (UK) Ltd appealed the decision. The EPO Technical Board of Appeals heard arguments related to the appeal on January 8, 2019 and the product claims of the patent were held invalid. The method of manufacture claims was remitted to the EPOOD for further consideration,

and remain enforceable. We have a divisional application pending that claims priority from the ‘759 patent where we are pursuing product claims of varying scope. European Patent No. 1962805, which expires approximately five months after the ‘759 patent (December 5, 2026 vs. July 19, 2026), also includes claims related to ARIKAYCE and its use in treating NTM lung disease. All of our issued European patents have expiration dates that would fall within the regulatory exclusivity period for ARIKAYCE, should ARIKAYCE ultimately gain approval by the EMA.

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

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

INS1007 Patents

Through our agreement with AstraZeneca, we have licensed US Patent Nos. 9,522,894 and 9,815,805, which have claims directed to INS1007 and methods for using INS1007. Each expires January 21, 2035 (not taking into account any potential patent term extension). Counterpart patent applications are pending throughout the world and a continuation application is pending in the US.

INS1009 Patents

We own US Patent No. 9,255,064 (expires October 24, 2034), which is the first patent to issue with claims covering hexadecyl-treprostinil, the treprostinil component of INS1009. Other treprostinil prodrugs are also claimed and described in the patent. We also own US Patent No. 9,469,600, which has claims directed to INS1009 and other treprostinil prodrug formulations and expires October 24, 2034. We also own US Patent No. 10,010,518, which has claims directed to methods of treating pulmonary hypertension, including PAH, with INS1009 and other treprostinil prodrug formulations and expires October 24, 2034. Counterpart patent applications to these US Patents are pending in Europe, Japan and other foreign jurisdictions.

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

Trademarks

In addition to our patents and trade secrets, we have filed applications to register certain trademarks in the US and/or abroad, including INSMED and ARIKAYCE. At present, we have received a registration for the INSMED and ARIKAYCE marks from the US Patent and Trademark Office (USPTO). We have also received foreign notices of allowance or registrations for the INSMED and ARIKAYCE marks, among others. The European Medicines Agency (EMA) has indicated it has no objection to our use of the name ARIKAYCE, and the FDA has approved our use of the name ARIKAYCE as the trade name for amikacin liposome inhalation suspension. Our ability to obtain and maintain trademark registrations will in certain geographical locations depend on making use of the mark in commerce on or in connection with our products and approval of the trademarks for our products by regulatory authorities in each country.

License and Other Agreements

ARIKAYCE-related Agreements

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

PARI Pharma GmbH

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

We have certain obligations under this licensing agreement in relation to specified licensed indications. With respect to CF, we are obligated to use commercially reasonable efforts to develop, obtain regulatory and reimbursement

approval, market and sell ARIKAYCE in two or more major European countries. With respect to NTM and bronchiectasis, we have specific obligations to use commercially reasonable efforts to achieve certain developmental and regulatory milestones by set deadlines. Additionally, for NTM, we are obligated to use commercially reasonable efforts to achieve certain commercial milestones in the US and Europe. The consequences of our failing to use commercially reasonable efforts to achieve these milestones are context-specific, but include ending PARI's non-compete obligation, making the license non-exclusive and

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terminating the license, in each case with respect to the applicable indication. Termination of the licensing agreement or loss of exclusive rights may occur if we fail to meet our obligations, including payment of royalties to PARI, or if we do not meet certain milestones contained in the licensing agreement such as obtaining marketing approval in an EU country.

Under the licensing agreement, we paid PARI an upfront license fee and milestone payments. Upon FDA acceptance of our NDA and the subsequent FDA approval of ARIKAYCE, we paid PARI additional milestone payments of €1.0 million and €1.5 million, respectively. In addition, PARI is entitled to receive future milestone payments up to €0.5 million in cash based on achievement of first receipt of marketing approval in a major EU country for ARIKAYCE and the device. In October 2017, we exercised an option to buy-down the royalties payable to PARI. PARI is now entitled to receive royalty payments in the mid-single digits on the annual global net sales of ARIKAYCE pursuant to the licensing agreement, subject to certain specified annual minimum royalties.

This licensing agreement will remain in effect on a country-by-country basis until the final royalty payments have been made with respect to the last country in which ARIKAYCE is sold, or until the agreement is otherwise terminated by either party. We have the right to terminate this licensing agreement upon written notice for PARI's uncured material breach, if PARI is the subject of specified bankruptcy or liquidation events, or if PARI fails to reach certain specified obligations. PARI has the right to terminate this licensing 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.

In July 2014, we entered into a Commercialization Agreement with PARI for the manufacture and supply of Lamira nebulizer systems and related accessories (the Device) as optimized for use with ARIKAYCE. Under the Commercialization Agreement, PARI manufactures the Device except in the case of certain defined supply failures, when we will have the right to make the Device and have it made by third parties (but not certain third parties deemed under the Commercialization Agreement to compete with PARI). The Commercialization Agreement has an initial term of 15 years that began to run in October 2018 (the Initial Term). The term of the Commercialization Agreement may be extended by us for an additional five years by providing written notice to PARI at least one year prior to the expiration of the Initial Term.

Althea

In September 2015, we entered into a Commercial Fill/Finish Services Agreement (the Fill/Finish Agreement) with Althea to produce, on a non-exclusive basis, ARIKAYCE in finished dosage form at a 50 kg scale. We are obligated to pay a minimum of $2.7 million for the batches of ARIKAYCE produced by Althea each calendar year during the term of the Fill/Finish Agreement. The Fill/Finish Agreement became effective as of January 1, 2015, and, following an extension in 2018, will remain in effect through December 31, 2021. The Fill/Finish Agreement may be extended for additional two-year periods upon mutual written agreement of the Company and Althea at least one year prior to the expiration of its then-current term. We have expensed at least the required minimum in each year of the contract. Either we or Althea may terminate the Fill/Finish Agreement upon the occurrence of certain events, including (i) material breach of the Fill/Finish Agreement by either party, provided such breach is not cured within 30 days after receipt by the breaching party of written notice of the breach or (ii) insolvency or bankruptcy of the other party. In addition, we may terminate the Fill/Finish Agreement without cause with 12 months' prior written notice to Althea, and Althea may terminate the Agreement without cause with 24 months' prior written notice to us.

Therapure

In February 2014, we entered into a contract manufacturing agreement with Therapure for the manufacture of ARIKAYCE, on a non-exclusive basis, at a 200 kg scale. Pursuant to the agreement, we collaborated with Therapure to construct a production area for the manufacture of ARIKAYCE in Therapure's existing manufacturing facility in Mississauga, Ontario, Canada. The agreement has an initial term of five years, which began in October 2018, and will renew automatically for successive periods of two years each, unless terminated by either party by providing the required two years' prior written notice to the other party. Notwithstanding the foregoing, the parties have rights and obligations under the agreement prior to the commencement of the initial term. Under the agreement, we are obligated

to pay certain minimum amounts for the batches of ARIKAYCE produced each calendar year. The agreement allows for termination by either party upon the occurrence of certain events, including (i) the material breach by the other party of any provision of the agreement or the quality agreement expected to be entered into between the parties, and (ii) the default or bankruptcy of the other party. In addition, we may terminate the agreement for any reason upon no fewer than 180 days' advance notice.

Patheon and related agreements

In October 2017, we entered into certain agreements with Patheon related to the increase of our long-term production capacity for ARIKAYCE. The agreements provide for Patheon to manufacture and supply ARIKAYCE for our anticipated commercial needs. Under these agreements, we are required to deliver to Patheon the required raw materials, including active pharmaceutical ingredients, and certain fixed assets needed to manufacture ARIKAYCE. Patheon's supply obligations will

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commence once certain technology transfer and construction services are completed. Our manufacturing and supply agreement with Patheon will remain in effect for a fixed initial term, after which it will continue for successive renewal terms unless either we or Patheon have given written notice of termination. The technology transfer agreement will expire when the parties agree that the technology transfer services have been completed. The agreements may also be terminated under certain other circumstances, including by either party due to a material uncured breach of the other party or the other party's insolvency. These early termination clauses may reduce the amounts due to the relevant parties. The investment in our long-term production capacity build-out, including under the Patheon agreements and related agreements or purchase orders with third parties for raw materials and fixed assets, is estimated to be approximately $60 million.

SynteractHCR, Inc. (Synteract)

We entered into a services agreement with Synteract pursuant to which we retained Synteract to perform implementation and management services in connection with the CONVERT study. We may terminate the services agreement or any work order for any reason and without cause with 30 days' written notice. Either party may terminate the agreement in the event of a material breach or bankruptcy petition by the other party or, if any approval from a regulatory authority is revoked, suspended or expires without renewal. We anticipate that aggregate costs relating to all work orders for the CONVERT study will be approximately $48 million over the period of the study. In April 2015, we entered into a work order with Synteract to perform implementation and management services for the 312 study.

Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT)

In 2004 and 2009, we entered into research funding agreements with CFFT whereby we received $1.7 million and $2.2 million for each respective agreement in research funding for the development of ARIKAYCE. If ARIKAYCE becomes an approved product for certain infections in CF patients or such infections in human pulmonary disease in the US, we will owe a payment to CFFT of up to $13.4 million that is payable over a three-year period after regulatory approval in the US. Furthermore, if certain global sales milestones are met within five years of the drug commercialization, we would owe additional payments of $3.9 million. Under the 2009 agreement, in the event we terminate development of ARIKAYCE for CF prior to first commercial sale of a product containing ARIKAYCE for a period of 360 continuous days, and such termination is not for reasons outside of our reasonable control, then at CFFT's election and within 180 days of such termination, CFFT (1) may elect to develop ARIKAYCE for CF and (2) will have the right to receive from us an exclusive (subject to certain exceptions), royalty-free, sub-licensable license to use, develop, sell and commercialize a product containing ARIKAYCE in the treatment of certain infections in CF patients or pulmonary disease associated with CF.

INS1007-related Agreements

Syneos Health

We entered into a services agreement with Syneos Health (Syneos) pursuant to which we retained Syneos to perform implementation and management services in connection with the WILLOW study. We may terminate the services agreement or any work order for any reason and without cause with 30 days' written notice. Either party may terminate the agreement in the event of a material breach or bankruptcy petition by the other party or, if any approval from a regulatory authority is revoked, suspended or expires without renewal. We anticipate that aggregate costs relating to all work orders for the WILLOW study will be approximately $21 million over the period of the study.

AstraZeneca

In October 2016, we entered into the AZ License Agreement, pursuant to which AstraZeneca granted us exclusive global rights for the purpose of developing and commercializing AZD7986 (renamed INS1007). In consideration of the licenses and other rights granted by AstraZeneca, we made an upfront payment of $30.0 million in late October 2016. We are obligated to make a series of contingent milestone payments to AstraZeneca totaling up to an additional $85.0 million upon the achievement of clinical development and regulatory filing milestones. If we elect to develop INS1007 for a second indication, we will be obligated to make an additional series of contingent milestone payments totaling up to $42.5 million. We are not obligated to make any additional milestone payments for additional indications. In addition, we have agreed to pay AstraZeneca tiered royalties ranging from a high single-digit to

mid-teens on net sales of any approved product based on INS1007 and one additional payment of $35.0 million upon the first achievement of $1 billion in annual net sales. The AZ License Agreement provides AstraZeneca with the option to negotiate a future agreement with us for commercialization of INS1007 in chronic obstructive pulmonary disease or asthma. If we fail to comply with our obligations under our agreements with AstraZeneca (including, among other things, if we fail to use commercially reasonable efforts to develop and commercialize a product based on INS1007, or we are subject to a bankruptcy or insolvency), AstraZeneca would have the right to terminate the license.

Competition

The biotechnology and pharmaceutical industries are highly competitive. We face potential competitors from many different areas including commercial pharmaceutical, biotechnology and device companies, academic institutions and

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scientists, other smaller or earlier stage companies and non-profit organizations developing anti-infective drugs and drugs for respiratory diseases. Many of these companies have greater human and financial resources and may have product candidates in more advanced stages of development and may reach the market before our product candidates. Competitors may develop products that are more effective, safer or less expensive or that have better tolerability or convenience. We also may face generic competitors where third-party payors will encourage use of the generic products. Although we believe that our formulation delivery technology, respiratory and anti-infective expertise, experience and knowledge in our specific areas of focus provide us with competitive advantages, these potential competitors could reduce our commercial opportunity. Additionally, there currently are, and in the future there may be, already-approved products for certain of the indications for which we are developing, or in the future may choose to develop, product candidates. For instance, PAH is a competitive indication with established products, including other formulations of treprostinil.

NTM lung disease competitive overview

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

Government Regulation

Orphan Drug Designation

United States

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

Orphan drug designation qualifies the sponsor for various development incentives of the ODA, including tax credits for qualified clinical testing, and a waiver of the PDUFA application fee (unless the application seeks approval for an indication not included in the orphan drug designation). Orphan drug designation also affords the company a period of exclusivity for the orphan indication upon approval of the drug. Specifically, the first NDA applicant with an FDA orphan drug designation for a particular active moiety to receive FDA approval of the drug for an indication covered by the orphan designation is entitled to a seven-year exclusive marketing period, often referred to as orphan drug exclusivity, in the US for that drug in that indication. A product that has several separate orphan designations may have several separate exclusivities for separate orphan indications. During the orphan drug exclusivity period, the FDA may not approve any other applications to market the same drug for the same indication for use, except in limited circumstances, such as a showing of clinical superiority to the product that has orphan drug exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition or the same drug for a different disease or condition, and it does not alter the timing or scope of the regulatory review and approval process; the sponsor must still submit evidence from clinical and non-clinical studies sufficient to demonstrate the safety and effectiveness of the drug.

European Union

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

proposed orphan drug will be of significant benefit to patients. The European Commission has granted an orphan designation for ARIKAYCE for the treatment of NTM lung disease.

If a drug with an orphan drug designation subsequently receives a marketing authorization for a therapeutic indication which is covered by such designation, the drug is entitled to orphan exclusivity. Orphan exclusivity means that the EMA or a national medicines agency may not accept another application for authorization, or grant an authorization, for a same or similar drug for the same therapeutic indication. Competitors may receive such a marketing authorization despite orphan exclusivity, provided that they demonstrate that the existing orphan product is not supplied in sufficient quantities or that the 'second' drug or biologic is clinically superior to the existing orphan product. The 'second' drug may but need not have an

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orphan designation as well. The period of orphan exclusivity is ten years, which can be extended by two years where an agreed pediatric investigation plan has been implemented. The exclusivity period may also be reduced to six years if the designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Each orphan designation carries the potential for one market exclusivity for all the therapeutic indications that are covered by the designation. A product that has several separate orphan designations may have several separate market exclusivities.

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

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

Japan

The Ministry of Health, Labour and Welfare (MHLW) may, after hearing the opinion of the Pharmaceutical Affairs and Food Sanitation Council, grant orphan drug designation to a drug intended to treat a rare disease or condition if the drug meets the following conditions: (i) the number of target patients is less than 50,000 in Japan, (ii) the necessity of orphan drug designation is high from a medical point of view, (iii) there are sufficient theoretical grounds to use the drug for the target disease, and (iv) the plan for development of the drug is appropriate. Even if a drug is granted orphan drug designation, however, it does not always receive the manufacturing and marketing approval that is necessary for the drug to be sold or marketed in Japan. ARIKAYCE did not qualify for orphan drug designation in Japan due to the estimated number of NTM patients in Japan exceeding 50,000.

Drug Approval

United States

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

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, formulation and toxicity, and pharmacology, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements including the FDA's good laboratory practices (GLP) regulations and the US Department of Agriculture's regulations implementing the Animal Welfare Act. An Investigational New Drug (IND) sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature, and a proposed clinical trial protocol, among other things, to the FDA as part of an IND application. Certain non-clinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not

result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects (healthy volunteers or patients) under the supervision of a qualified investigator. Clinical trials must be conducted (i) in compliance with all applicable federal regulations and guidance, including those pertaining to good clinical practice (GCP) standards that are meant to protect the rights, safety, and welfare of human subjects and to define the roles of clinical trial sponsors, investigators, and monitors as well as (ii) under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring

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safety, and the effectiveness criteria to be evaluated. Each protocol involving testing of a new drug in the US (whether in patients or healthy volunteers) must be included as a submission to the IND, and the FDA must be notified of subsequent protocol amendments, including new protocols. In addition, the protocol must be reviewed and approved by an institutional review board (IRB), and all study subjects must provide informed consent. Typically, before any clinical trial, each institution participating in the trial will require review of the protocol before the trial commences at that institution. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and there are additional, more frequent reporting requirements for certain adverse events.

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

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential pre-approval phases, but the phases may overlap or be combined. In Phase 1, short term (typically less than a few months) testing is conducted in a small group of subjects (typically 20-100), who may be patients with the target disease or condition or healthy volunteers, to evaluate its safety, determine a safe dosage range, and identify side effects. In Phase 2, the drug is given to a larger group of subjects (typically up to several hundred) with the target condition to further evaluate its safety and gather preliminary evidence of efficacy. Phase 3 studies typically last between several months and two years. In Phase 3, the drug is given to a large group of subjects with the target disease or condition (typically several hundred to several thousand), often at multiple geographical sites, to confirm its effectiveness, monitor side effects, and collect data to support drug approval. Only a small percentage of investigational drugs complete all three phases of development and obtain marketing approval.

NDA

After completion of the required clinical testing, an NDA can be prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the US. The NDA is a large submission that must include, among other things, the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls. The application also includes representative samples, copies of the proposed product labeling, patent information, and a financial certification or disclosure statement. The cost of preparing and submitting an NDA is substantial. Additionally, under federal law (as amended by the most recent reauthorization of the Prescription Drug User Fee Act (PDUFA VI) in the FDA Reauthorization Act of 2017), most NDAs are subject to a substantial application fee and, upon approval, the applicant will be assessed an annual prescription drug program fee, both of which are adjusted annually. NDAs for orphan drugs are not subject to an application fee, unless the application includes an indication other than the orphan-designated indication. FDA also has the authority to grant waivers of certain user fees, pursuant to the FDCA.

The FDA has 60 days from its receipt of an NDA to determine whether the application is accepted for filing based on the FDA's threshold determination that it is sufficiently complete to permit substantive review. Once the submission is accepted for filing, the FDA begins a substantive review. The FDA may refer applications for novel drug products or drug products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes outside clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

Before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Additionally, the FDA will typically inspect the facility or the facilities at which the drug is manufactured. FDA will not approve the product unless compliance with current good manufacturing practices (cGMP) is satisfactory and the NDA contains data that provide substantial evidence of effectiveness for the proposed indication, generally consisting of adequate and well-controlled clinical investigations, and that the drug is safe for use under the conditions of use in the proposed labeling. The FDA also reviews the proposed labeling submitted with the NDA and typically requires changes in the labeling text.

After the FDA evaluates the NDA and the manufacturing and testing facilities, it issues either an approval letter or a complete response letter. Complete response letters generally outline the deficiencies in the submission and delineate the additional testing or information needed in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. An approval letter, which may specify post approval requirements, authorizes commercial marketing of the drug for the approved indication or indications and the other conditions of use set out in the approved prescribing information. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing. Under priority review status, the FDA has 180 days from either the 60 day filing date (in the case of NME NDA submissions) or the date of receipt of the NDA (in the case of non-NME original NDA submissions) to issue either an approval letter or a complete response letter, unless the review period is adjusted by mutual agreement between the FDA and the

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applicant or as a result of the applicant submitting a major amendment. The FDA's current performance goals call for the FDA to complete review of 90 percent of standard (non-priority) NDAs within 10 months and priority NDAs within six months of NDA filing or receipt.

As a condition of NDA approval, the FDA may require substantial post-approval testing, known as phase 4 studies, to be conducted in order to gather additional information on the drug's effect in various populations and any side effects associated with long-term use. Beyond routine post marketing safety surveillance, the FDA may require specific additional surveillance to monitor the drug's safety or efficacy and may impose other conditions, including labeling restrictions that can materially affect the potential market and profitability of the drug. As a condition of approval, or after approval, the FDA also may require submission of a risk evaluation and mitigation strategy (REMS) or a REMS with elements to assure safe use to mitigate any identified or suspected serious risks. The REMS may include medication guides, physician communication plans, assessment plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools. Further post-approval requirements are discussed below.

Expedited Review and Approval of Eligible Drugs

Under the FDA's accelerated approval program, the FDA may approve certain drugs for serious or life-threatening conditions on the basis of a surrogate or intermediate endpoint that is reasonably likely to predict clinical benefit, which can substantially reduce time to approval. A surrogate endpoint used for accelerated approval is a marker—a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than irreversible morbidity and mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit. The FDA bases its decision on whether to accept the proposed surrogate or intermediate clinical endpoint on the scientific support for that endpoint.

As a condition of accelerated approval, the FDA typically requires certain post-marketing clinical studies to verify and describe clinical benefit of the product, and may impose restrictions on distribution to assure safe use. Post marketing studies would usually be required to be studies already underway at the time of the accelerated approval. In addition, promotional materials for an accelerated approval drug to be used in the first 120 days post-approval must be submitted to the FDA prior to approval, and materials to be used after that 120-day period must be submitted 30 days prior to first use. If the required post-marketing studies fail to verify the clinical benefit of the drug, or if the applicant fails to perform the required post-marketing studies with due diligence, the FDA may withdraw approval of the drug under streamlined procedures in accordance with the agency's regulations. The agency may also withdraw approval of a drug if, among other things, the promotional materials for the product are false or misleading, or other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

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

Priority review applies to an application (both original and efficacy supplement) for a drug that treats a serious condition and that, if approved, would provide a significant improvement in safety or effectiveness. It also applies to

any supplement that proposes a labeling change pursuant to a report on a pediatric study. A request for priority review is submitted at the time of NDA or supplemental NDA submission. The FDA must respond within 60 days of receipt of the request. If granted, the review time is shortened from the standard 10 months to 6 months, beginning either at the 60 day filing date (in the case of NME NDA submissions) or the date of receipt (in the case of non-NME original NDA submissions).

Breakthrough therapy designation applies to a drug that is intended to treat a serious condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. It can be requested with the IND submission and ideally no later than the end-of-phase 2 meeting. The FDA must respond within 60 days of receipt of the request. If granted, the applicant receives intensive guidance on efficient drug development, intensive involvement of senior managers and experienced review and regulatory health project

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management staff in a proactive, collaborative, cross-disciplinary review, rolling review, and other actions to expedite review. Designation may be rescinded if the product no longer meets the criteria for breakthrough therapy designation.
Drugs that are designated as QIDPs are eligible for priority review and fast track designation, and well as market exclusivity. A product is eligible if it is an antibacterial or anti-fungal drug for human use that is intended to treat serious or life-threatening infections, including: those caused by an anti-bacterial or anti-fungal resistant pathogen, including novel or emerging infectious pathogens; or caused by qualifying pathogens listed by the FDA. A drug sponsor may request that the FDA designate its product as a QIDP at any time prior to NDA submission. The FDA must make a QIDP determination within 60 days of receiving the designation request. ARIKAYCE has been designated as a QIDP for NTM lung disease.
Additionally, the FDA may approve eligible drugs under the LPAD. A product is eligible if it is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs, the drug otherwise meets the standards of approval, and the FDA receives a written request from the sponsor to approve the drug under this pathway. An antibacterial or antifungal drug approved through this pathway may follow a streamlined clinical development program involving smaller, shorter, or fewer clinical trials. Approval is based on a benefit-risk assessment in the intended limited population, taking into account the severity, rarity, or prevalence of the infection the drug is intended to treat and the availability or lack of alternative treatment for the patient population. Such drugs may not have favorable benefit-risk profiles in a broader population. Drugs approved under LPAD are subject to additional regulatory requirements, including labeling and advertising statements regarding the limited population and submission of promotional materials to the FDA at least 30 days prior to dissemination. The FDA may remove these additional requirements if the agency approves the drug for a broader population.

Exclusivities

After NDA approval, owners of relevant drug patents may apply for up to a five-year patent extension on a single patent. The allowable patent term extension is calculated as half of the drug's testing phase (the time between IND application and NDA submission) and all of the review phase (the time between NDA submission and approval) up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years. For patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the USPTO must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which an NDA has not been submitted.
A variety of non-patent exclusivity periods are available under the FDCA that can delay the submission or approval of certain applications for competing products.
A five-year period of non-patent exclusivity within the US is granted to the first applicant to gain approval of an NDA for a new chemical entity (NCE). An NCE is a drug that contains no active moiety (the molecule or ion responsible for the action of the drug substance) that has been approved by the FDA in any other application submitted under section 505(b) of the FDCA. During the exclusivity period for a NCE, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company that references (i.e., relies on FDA prior approval of) the NCE drug. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement with respect to a patent listed with the FDA for the reference NDA.
A three-year period of non-patent exclusivity is granted for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the sponsor that were essential to approval of the application, for example, for new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations, which means that the FDA may approve applications for other versions of the original, unmodified drug product. Where this form of exclusivity applies, it prevents FDA approval of an ANDA or 505(b)(2) NDA subject to the exclusivity for the three-year period; however, the FDA may

accept and review ANDAs or 505(b)(2) NDAs during the three-year period.

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

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

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Medical Device Regulation

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

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

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

Combination Products

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

The FDA is divided into various Centers, which each have authority over a specific type of product. NDAs are reviewed by personnel within the Center for Drug Evaluation and Research, while device applications and premarket notifications are reviewed by the Center for Devices and Radiological Health. Combination products, such as drug/device combinations, generally will be reviewed by the Center that regulates the product's primary mode of action (PMOA), which is the single mode of a combination product that provides the most important therapeutic action of the combination product. If the PMOA is unclear or in dispute, a sponsor may file a Request for Designation with FDA’s Office of Combination Products (OCP), which will render a determination and assign a lead Center. OCP generally assigns jurisdiction based on PMOA. If there are two independent modes of action, neither of which is subordinate to the other, the FDA makes a determination as to which Center to assign the product based on consistency with other combination products raising similar types of safety and effectiveness questions or to the Center with the most expertise in evaluating the most significant safety and effectiveness questions raised by the combination product.

When evaluating an application for a combination product, a lead Center may consult other Centers and apply the standards that would be applicable but still retain reviewing authority, or it may assign review of a specific section of the application to another Center, delegating its review authority for that section. Depending on the type of combination product, approval or clearance could be obtained through submission of a single marketing application or through separate applications for the individual constituent parts (e.g., an NDA for the drug and a premarket notification for the device). The FDCA directs the FDA to conduct a review of a combination product under a single marketing application whenever appropriate. The agency has the discretion to require separate applications to more than one Center, and applicants may choose to submit separate applications for constituent parts of a combination (unless the FDA determines one application is necessary). One reason to submit multiple applications is if the applicant wishes to receive some benefit that accrues only from approval under a particular type of application, like new drug product exclusivity. If multiple applications are submitted, each application is generally reviewed by the Center with authority over each application type. For combination products that contain an approved constituent part (such as a drug-device combination product in which the device has previously received clearance), the FDA may require that the application(s) include only such information as is necessary to meet the standard for clearance or approval, taking into account any prior finding of safety or effectiveness for the approved constituent part.

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

Disclosure of Clinical Trial Information

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

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to two years if the sponsor is seeking approval of the product or a new indication. Competitors may use this publicly-available information to gain knowledge regarding the progress of development programs.

Other Post-approval Regulatory Requirements

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

The FDA regulates the content and format of prescription drug labeling, advertising, and promotion, including direct-to-consumer advertising and promotional Internet communications. FDA also establishes parameters for permissible non-promotional communications between industry and the medical community, including industry-supported scientific and educational activities. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion for uses not consistent with the approved labeling, and a company that is found to have improperly promoted off-label uses or otherwise not to have met applicable promotion rules may be subject to significant liability under both the FDCA and other statutes, including the False Claims Act.

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

All aspects of pharmaceutical manufacture must conform to cGMPs after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA during which the FDA inspects manufacturing facilities to assess compliance with cGMPs. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMPs.

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

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

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

European Union

MAA

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

Under the centralized procedure, the Committee for Medicinal Products for Human Use (CHMP) is required to adopt an opinion on a valid application within 210 days, excluding clock stops when additional information is to be provided

by the applicant in response to questions. More specifically, on day 120 of the procedure, once the CHMP has received the preliminary assessment reports and opinions from the Rapporteur and Co-Rapporteur designated by the CHMP, it adopts a list of questions, which are sent to the applicant together with the CHMP's overall conclusions. Applicants then have three months to respond to the CHMP (and can request a three-month extension). The Rapporteur and Co-Rapporteur assess the applicant's replies, revise the assessment report as necessary and may prepare a list of outstanding issues. The revised assessment report and list of outstanding issues are sent to the applicant together with the CHMP's recommendation by day 180 of the procedure. Applicants then have one month to respond to the CHMP (and can request a one or two-month extension). The Rapporteur and

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Co-Rapporteur assess the applicant's replies, submit them for discussion to the CHMP and prepare a final assessment report. Once its scientific evaluation is completed, the CHMP gives a favorable or unfavorable opinion as to whether to grant the marketing authorization. After the adoption of the CHMP opinion, a decision must be adopted by the European Commission, after consulting the Standing Committee of the Member States. The European Commission prepares a draft decision and circulates it to the member states; if the draft decision differs from the CHMP opinion, the Commission must provide detailed explanations. The European Commission adopts a decision within 15 days of the end of the consultation procedure.

Accelerated Procedure, Conditional Approval and Approval Under Exceptional Circumstances

Various programs, including accelerated procedure, conditional approval and approval under exceptional circumstances, are intended to expedite or simplify the approval of drugs that meet certain qualifications. The purpose of these programs is to provide important new drugs to patients earlier than under standard approval procedures.

For drugs which are of major interest from the point of view of public health, in particular from the viewpoint of therapeutic innovation, applicants may submit a substantiated request for accelerated assessment. If the CHMP accepts the request, the review time is reduced from 210 to 150 days.

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

Conditional marketing authorizations may be granted for products designated as orphan medicinal products, if all of the following conditions are met: (1) the risk-benefit balance of the product is positive, (2) the applicant will likely be in a position to provide the required comprehensive clinical trial data, (3) the product fulfills unmet medical needs, and (4) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Conditional marketing authorizations are valid for one year, on a renewable basis until the holder provides a comprehensive data package. The granting of conditional marketing authorization depends on the applicant's ability to fulfill the conditions imposed within the agreed upon deadline. They are subject to "conditions", i.e. the holder is required to complete ongoing studies or to conduct new studies with a view to confirming that the benefit-risk balance is positive or to fulfill specific obligations in relation to pharmacovigilance. Once the holder has provided a comprehensive data package, the conditional marketing authorization is replaced by a 'regular' marketing authorization.

Marketing authorizations under exceptional circumstances may be granted where the applicant demonstrates that, for objective and verifiable reasons, they are unable to provide comprehensive data on the efficacy and safety of the drug under normal conditions of use. Such marketing authorizations are subject to certain conditions, in particular relating to safety of the drug, notification of incidents relating to its use or actions to be taken. They are valid for an indefinite period of time, but the conditions upon which they are based are subject to an annual reassessment in order to ensure that the risk-benefit balance remains positive.

Exclusivities

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

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

Medical Devices Regulations

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

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Medical devices are generally governed by Directive 93/42/EEC on Medical Devices that harmonizes the conditions for placing medical devices on the European market. This Directive however does not regulate certain important marketing aspects, such as advertising or pricing and reimbursement, which remain governed by national law. Directive 93/42 requires medical devices to meet the essential requirements which are enumerated in the annexes to the Directive. Compliance with those requirements is demonstrated by the CE mark as the manufacturer may only affix the CE mark if it may declare conformity with the essential requirement for each medical device that is marketed. Directive 93/42 provides recourse to harmonized European standards in order to facilitate compliance with the essential requirements. Harmonized standards provide a presumption of conformity with the essential requirements.

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

For classes of devices other than Class I, a manufacturer must have a Notified Body test and certify conformity of its design and production procedures or its products with the essential requirements of Directive 93/42. Certification takes the form of a certificate of conformity issued by the Notified Body, which is valid throughout the European Union. Upon certification by the Notified Body, the manufacturer affixes the CE mark to the medical device, which allows the product to move freely within the EU and thus prevents EU Member States from restricting sales and marketing of the devices, unless such measure is justified on the basis of evidence of non-compliance. Ultimately, the manufacturer is responsible for the conformity of the device with the essential requirements and for the affixing of the CE mark. The Lamira Nebulizer System is CE marked by PARI in the EU.

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

In May 2017, the EU adopted a new Medical Devices Regulation (EU) 2017/745 (MDR), which will repeal and replace Directive 93/42 with effect from May 26, 2020. The MDR envisages, among other things, stricter controls of medical devices, including strengthening of the conformity assessment procedures, increased expectations as regards clinical data for devices and pre-market regulatory review of high-risk devices. Under transitional provisions, medical devices with notified body certificates issued under Directive 93/42 prior to May 26, 2020 may continue to be placed on the market for the remaining validity of the certificate, until May 27, 2024 at the latest. After the expiry of any applicable transitional period, only devices that have been CE marked under the MDR may be placed on the market in the EU.

Japan

Under the Japanese regulatory system administered by the MHLW and the PMDA (which is responsible for product review and evaluations under the supervision of the MHLW), pre-marketing approval and clinical studies are required for all pharmaceutical products. The Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960) requires a license for marketing authorization when importing to Japan and selling pharmaceutical products manufactured in other countries. It also requires a foreign manufacturer to get each of its manufacturing sites certified as a manufacturing site of pharmaceutical products to be marketed in Japan. To receive a license for marketing authorization, the manufacturer or seller must, at the very least, employ certain manufacturing marketing, quality and safety personnel. A license for marketing authorization may not be granted if the quality management methods and post marketing safety management methods applied with respect to

the pharmaceutical product fail to conform to the standards stipulated in the ordinances promulgated by the MHLW. To obtain manufacturing/marketing approval for a new product, a Company must submit an application for approval to the MHLW with results of nonclinical and clinical studies to show the quality, efficacy and safety of the product candidate. A data compliance review, on-site inspection for good clinical practice, audit and detailed data review for compliance with current good manufacturing practices are undertaken by the PMDA. The application is then discussed by the committees of the Pharmaceutical Affairs and Food Sanitation Council. Based on the results of these reviews, the final decision on approval is made by the MHLW. The time required for the approval process varies depending on the product, but it can take years. The product also needs approval for pricing to be applied for redemption of health insurance. The medical products which once are approved and marketed are also subject to regular post-marketing vigilance of safety and quality under the standards of Good Manufacturing Practice. In Japan, the National Health Insurance

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system maintains a Drug Price List specifying which pharmaceutical products are eligible for reimbursement, and the MHLW sets the prices of the products on this list. After receipt of marketing approval, negotiations regarding the reimbursement price with the MHLW would begin. Price would be determined within 60 to 90 days unless the applicant disagrees, which may result in extended pricing negotiations. The government generally introduces price cut rounds every other year and also mandates price decreases for specific products. New products judged innovative or useful, that are indicated for pediatric use, or that target orphan or small population diseases, however, may be eligible for a pricing premium. The government has also promoted the use of generics, where available.

Pediatric Information

United States

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

European Union

In the EU, new drugs (i.e. drugs containing a new active substance) for adults, must also be tested in children. This mandatory pediatric testing is carried out through the implementation of a pediatric investigation plan, or PIP, which is proposed by the applicant and approved by the EMA. A PIP contains all the studies to be conducted and measures to be taken in order to support the approval of the new drug, including pediatric pharmaceutical forms, in all subsets of the pediatric population. Validation of the MAA for adults is subject to the implementation of the PIP, subject to one or more waivers or deferrals. On the one hand, the PIP may allow a deferral for one or more of the studies or measures included therein in order not to delay the approval of the drug in adults, and, on another hand, the EMA may grant either a product-specific waiver for the (adult) disease/condition or one or more pediatric subsets or a class waiver for the disease/condition. PIPs are subject to modifications from time to time, when they no longer are workable. Prior to obtaining the validation of a MAA for adults, the applicant has to demonstrate compliance with the PIP at the time of submission of the application. In the case of orphan medicinal products, completion of an approved PIP can result in an extension of the market exclusivity period from ten to twelve years.

Japan

In Japan, there is no statutory rule which imposes any obligation on pharmaceutical manufacturers engaging in pediatric drug development. However, the guidelines of the MHLW (Handling of Pharmaceuticals during the Reexamination Interval Period (Issue No. 107, February 1, 1999 and No. 1324, December 27, 2000)) state as follows: (i) since information on pediatric patients obtained in clinical trials may be limited, the MHLW recommends that pharmaceutical manufacturers conduct adequate post-marketing surveillance during the reexamination interval period and collect as much information as possible for proper use of drugs for pediatric patients; and (ii) if a pharmaceutical manufacturer plans to conduct a clinical trial to set the dose of a pediatric drug to prepare application for manufacturing/marketing approval or after receiving the same approval, the reexamination interval period may be extended up to 10 years. In addition, since 2010 the MHLW has been promoting the development of children’s drugs that have been approved for use in Europe and the US but are not yet approved in Japan, so that they can be used as early as possible in Japan as well.

Regulation Outside the US, Europe and Japan

In addition to regulations in the US, Europe and Japan, we will be subject to a variety of regulations in other jurisdictions governing clinical studies of our candidate products, including medical devices. Regardless of whether we obtain FDA approval for a product candidate, we must obtain approval of the product candidate (including a medical device) by the comparable regulatory authorities of countries outside the US before we can commence clinical studies or marketing of the product candidate in those countries. The requirements for approval and the approval process vary from country to country, and the time may be longer or shorter than that required for FDA approval. Under certain harmonized medical device approval/clearance regulations outside the US, reference to US clearance permits fast-tracking of market clearance. Other regions are harmonized with EU standards, and therefore recognize the CE mark as a declaration of conformity to applicable standards.

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Furthermore, we must obtain any required pricing approvals in addition to regulatory approval prior to launching a product candidate in the approving country.

Early Access Programs

Under EU law, member states are authorized to adopt national legal regimes for the supply or use of non-authorized drugs in case of therapeutic needs. The most common national legal regimes are compassionate use programs and named patient sales, but other national regimes for early access may be available, depending on the member state. For drugs that must be approved through the centralized procedure, such as orphan drugs, compassionate use programs are also regulated at the European level. ARIKAYCE is available in certain countries under early access programs.

Special programs can be set up to make available to patients with an unmet medical need a promising drug which has not yet been authorized for their condition (compassionate use). As a general rule, compassionate use programs can only be put in place for drugs or biologics that are expected to help patients with life-threatening, long-lasting or seriously disabling illnesses who currently cannot be treated satisfactorily with authorized medicines, or who have a disease for which no medicine has yet been authorized. The compassionate use route may be a way for patients who cannot enroll in an ongoing clinical trial to obtain treatment with a potentially life-saving medicine. Compassionate use programs are coordinated and implemented by the EU member states, which decide independently how and when to open such programs according to national rules and legislation. Generally, doctors who wish to obtain a promising drug for their seriously ill patients will need to contact the relevant national authority in their respective country and follow the procedure that has been set up. Typically, the national authority keeps a register of the patients treated with the drug within the compassionate use program, and a system is in place to record any side effects reported by the patients or their doctors. Orphan drugs very often are subject to compassionate use programs due to their very nature (rare diseases are life-threatening, long-lasting or seriously disabling diseases) and the long time required for both their approval and effective marketing.

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

Reimbursement of Pharmaceutical Products

In the US, many independent third-party payors, as well as the Medicare and state Medicaid programs, reimburse dispensers of pharmaceutical products. Medicare is the federal program that provides health care benefits to senior citizens and certain disabled and chronically ill persons. Medicaid is the need-based federal and state program administered by the states to provide health care benefits to certain persons.

As one of the conditions for obtaining Medicaid and, if applicable, Medicare Part B coverage for our marketed pharmaceutical products, we will need to agree to pay a rebate to state Medicaid agencies that provide reimbursement for those products. We will also have to agree to sell our commercial products under contracts with the Department of Veterans Affairs, Department of Defense, Public Health Service, and numerous other federal agencies as well as certain hospitals that are designated by federal statutes to receive drugs at prices that are significantly below the price we charge to commercial pharmaceutical distributors. These programs and contracts are highly regulated and will impose restrictions on our business. Failure to comply with these regulations and restrictions could result in adverse consequences such as civil money penalties, imposition of a Corporate Integrity Agreement and/or a loss of our ability to continue receiving Medicare and Medicaid reimbursement for our drugs. In January 2019, the Department of Health and Human Services released a proposed rule to reform the system of rebates paid to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers. We are currently reviewing the proposed rule, the impact of which is uncertain at this time.

Private healthcare payors also attempt to control costs and influence drug pricing through a variety of mechanisms, including through negotiating discounts with the manufacturers and through the use of tiered formularies and other mechanisms that provide preferential access to certain drugs over others within a therapeutic class. payors also set

other criteria to govern the uses of a drug that will be deemed medically appropriate and therefore reimbursed or otherwise covered.

The US President has indicated an interest in taking steps to lower drug prices, such as having the federal government negotiate drug prices with pharmaceutical manufacturers and/or in indexing certain federally reimbursement payments to international drug prices. In May 2018, the Administration issued "American Patients First," a multi-faceted blueprint to lower drug prices. The Administration has taken administrative steps to implement the blueprint, including through proposing sweeping demonstration projects aimed at putting downward pressure on drug prices. In addition, members of Congress have indicated an interest in legislative measures designed to lower drug costs. Drug pricing is an active area for

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regulatory reform at both the federal and state levels, and significant changes to current drug pricing and reimbursement structures in the US could be forthcoming

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

In Japan, drugs can be sold on the market if they undergo the PMDA's review of safety, effectiveness and quality and receive manufacturing/marketing approval. However, in order for drugs to be covered by the National Health Insurance, they must be included in a Drug Price List. The "Drug Pricing Organization," which is a division of the Central Social Insurance Medical Council (CSIMC), calculates the price of drugs, the general meeting of the CSIMC approves the calculated price, and the MHLW includes the drugs and the calculated price in the Drug Price List. After receiving manufacturing/marketing approval, drugs are included in the Drug Price List within 60 to 90 days unless the applicant disagrees, which may result in extended pricing negotiations. The MHLW updates the Drug Price List biennially after taking into account the survey result of the actual sales price of drugs and hearing the opinion of the CSIMC.

Fraud and Abuse and Other Laws

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

- The federal anti-kickback statute;
- The federal civil False Claims Act;
- The federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), as amended by the Health Information Technology for Economic and Clinical Health Act;
- The federal criminal false statements statute;
- The price reporting requirements under the Medicaid Drug Rebate Program and the Veterans Health Care Act of 1992;
- The federal Physician Payment Sunshine Act, being implemented as the Open Payments Program; and
- Analogous and similar state laws and regulations.

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

Employees

As of December 31, 2018, we had a total of 373 employees, including: 130 in research, clinical, regulatory, medical affairs and quality assurance; 31 in technical operations, manufacturing and quality control; 84 in general and administrative functions; and 128 in commercial activities. We had 339 employees in the US, 28 employees in Europe and 6 employees in Japan. We anticipate increasing our headcount in 2019.

None of our employees are represented by a labor union and we believe that our relations with our employees are generally good. Generally, our employees are at-will employees; however, we have entered into employment

agreements with certain of our executive officers.

Available Information

We file electronically with the SEC our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 (Exchange Act). We make available on our website at http://www.insmed.com, free of charge, copies of these reports as soon as reasonably practicable after filing, or furnishing them to, the SEC. The public can also obtain materials that we file with the SEC through the SEC's website at http://www.sec.gov.

Also available through our website's "Investor Relations Corporate Governance" page are charters for the Audit, Compensation and Nominations and Governance Committees of our board of directors, our Corporate Governance Guidelines,

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and our Code of Business Conduct and Ethics. We intend to satisfy the disclosure requirements regarding any amendment to, or waiver from, a provision of the Code of Business Conduct and Ethics by making disclosures concerning such matters available on our website.

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

Financial Information

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

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ITEM 1A. RISK FACTORS

Our business is subject to substantial risks and uncertainties. Any of the risks and uncertainties described below, either alone or taken together, could materially and adversely affect our business, financial condition, results of operations, prospects for growth, and the value of an investment in our common stock. In addition, these risks and uncertainties could cause actual results to differ materially from those expressed or implied by forward-looking statements contained in this Annual Report on Form 10-K (please read the Cautionary Note Regarding Forward-Looking Statements appearing at the beginning of this Annual Report on Form 10-K).

Risks Related to the Commercialization and Continued Approval of ARIKAYCE

Our prospects are highly dependent on the success of our only approved product, ARIKAYCE, which was approved in the United States (US) under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) and accelerated approval pathways. If we are unable to successfully commercialize or maintain approval for ARIKAYCE, our business, financial condition, results of operations and prospects and the value of our common stock will be materially adversely affected.

Our long-term viability and growth depend on the successful commercialization of ARIKAYCE, our only approved product, which has been approved in the US for the treatment of patients with refractory MAC lung disease as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options. We have invested and continue to invest significant efforts and financial resources in the launch of ARIKAYCE, and our ability to generate revenue from ARIKAYCE will depend heavily on successfully commercializing and obtaining full regulatory approval for ARIKAYCE by conducting an appropriate confirmatory post-marketing study. ARIKAYCE is our first commercial launch, and its successful commercialization and our receipt of full regulatory approval for ARIKAYCE in the US are subject to many risks.

The commercial success of ARIKAYCE will depend on the degree of market acceptance by physicians, patients, third-party payors and others in the health care community.

Despite receiving US Food and Drug Administration (FDA) approval of ARIKAYCE, the product may not gain, or over time may not retain, market acceptance by physicians, patients, third-party payors or others in the health care community. ARIKAYCE was the first product approved via the LPAD pathway, and there is limited information on how this approval may impact market acceptance of the product. If ARIKAYCE does not achieve and maintain an adequate level of acceptance, it is likely that we will not generate significant revenue or become profitable. The degree of market acceptance of ARIKAYCE, which we launched in the US early in the fourth quarter of 2018, is also dependent on a number of additional factors, including the following:

- The willingness of the target patient population to use, and of physicians to prescribe, ARIKAYCE;
- The efficacy and potential advantages of ARIKAYCE over alternative treatments;
- The risk and safety profile of ARIKAYCE, including, among other things, physician and patient concern regarding the boxed warning and other safety precautions resulting from its association with an increased risk of respiratory adverse reactions, and any adverse safety information that becomes available as a result of longer-term use of ARIKAYCE;
- Relative convenience and ease of administration;
- The ability of the patient to tolerate ARIKAYCE;
- The pricing of ARIKAYCE;
- The ability and willingness of the patient to pay out of pocket costs for ARIKAYCE, for example, co-payments;
- Sufficient third-party insurance coverage and reimbursement;
- The strength of marketing and distribution support and timing of market introduction of competitive products and treatments; and
- Publicity concerning ARIKAYCE or any potential competitive products and treatments.

Our efforts to educate physicians, patients, third-party payors and others in the health care community on the benefits of ARIKAYCE will require significant resources, which may be greater than those required to commercialize more established technologies and may never be successful.

We obtained regulatory approval of ARIKAYCE in the US through an accelerated approval process, and full approval will be contingent on successful completion of a confirmatory post-marketing study. Failure to obtain full approval or otherwise meet our post-marketing requirements and commitments would have a material adverse effect on our business.

The FDA approved ARIKAYCE under the LPAD and accelerated approval pathways, and full approval will be based on results from a post-approval confirmatory clinical trial. Accelerated approval allows drugs that (i) are being developed to

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treat a serious or life-threatening disease or condition and (ii) provide a meaningful therapeutic benefit over existing treatments to be approved substantially based on an intermediate endpoint or a surrogate endpoint that is reasonably likely to predict clinical benefit, rather than a clinical endpoint such as survival or irreversible morbidity. Accelerated approval of ARIKAYCE was supported by preliminary data from the Phase 3 CONVERT study, which evaluated the safety and efficacy of ARIKAYCE in adult patients with refractory MAC lung disease, using achievement of sputum culture conversion (defined as three consecutive negative monthly sputum cultures) by Month 6 as the primary endpoint.

The required confirmatory trial, which is currently under discussion with FDA, is proposed to be a randomized, double-blind, placebo-controlled clinical trial to assess and describe the clinical benefit of ARIKAYCE in patients with MAC lung disease. The trial will evaluate the effect of ARIKAYCE on a clinically meaningful endpoint, as compared to an appropriate control in the intended patient population of patients with MAC lung disease. Pursuant to the timetable agreed upon with the FDA, the study protocol is scheduled to be finalized during the first half of 2019, with trial results to be reported by 2024. There is little precedent for clinical development and regulatory expectations for agents to treat MAC lung disease. As a result, we may encounter challenges designing this trial, including developing and reaching agreement with the FDA on the appropriate clinical endpoints. We may encounter substantial delays in enrolling and conducting the trial, and we may not be able to enroll and conduct the trial in a manner satisfactory to the FDA or within the time period required by the FDA. If the confirmatory trial is not successful or we are unable to meet the timelines required by the FDA, the FDA could, among other things, withdraw its approval of ARIKAYCE. Separate from the confirmatory trial, additional results from ongoing and recently completed studies may affect the FDA's benefit-risk analysis for the product. Additionally, ARIKAYCE is subject to post-marketing commitments consisting of implementation of a healthcare provider communication plan, conducting a drug utilization assessment, and conducting further studies to identify an optimal quality control in vitro drug release method. Failure to meet post-marketing commitments may raise additional regulatory challenges.

We remain subject to substantial, ongoing regulatory requirements in the US related to ARIKAYCE, and failure to comply with these requirements could lead to enforcement action or otherwise materially harm our business.

ARIKAYCE is subject to a variety of manufacturing, packaging, storage, labeling, advertising, promotion, and record-keeping requirements, including requirements to:

- Conduct sales, marketing and promotion, scientific exchange, speaker programs, charitable donations and educational grant programs in compliance with federal and state laws;
- Disclose clinical trial results and payments to health care professionals and health care organizations on publicly available databases;
- Monitor and report complaints, adverse events and instances of failure to meet product specifications; and
- Comply with current good manufacturing practices (cGMP) and certain quality systems requirements for device components.

Failure to comply with these ongoing regulatory obligations could have significant negative consequences, including:

- Issuance of warning letters or untitled letters by FDA asserting that we are in violation of the law;
- Imposition of injunctions or civil monetary penalties or pursuit by regulators of civil or criminal prosecutions and fines against us or our responsible officers;
- Suspension or withdrawal of regulatory approval;
- Suspension or termination of ongoing clinical trials or refusal by regulators to approve pending marketing applications or supplements to approved applications;
- Seizure of products, required product recalls or refusal to allow us to enter into supply contracts, including government contracts, or to import or export products;
- Suspension of, or imposition of restrictions on, our operations, including costly new manufacturing requirements with respect to ARIKAYCE; and
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Negative publicity, including communications issued by regulatory authorities, which could negatively impact the perception of us or ARIKAYCE by patients, physicians, third-party payors or the health care community.

We provide financial assistance with out-of-pocket costs to patients enrolled in commercial health insurance plans. In addition, independent foundations may assist with out-of-pocket financial obligations. The ability of these organizations to provide assistance to patients is dependent on funding from external sources, and we cannot guarantee that such funding will be available at adequate levels, if at all. Patient assistance programs, whether provided directly by manufacturers or charitable foundations, have come under recent government scrutiny. If we are deemed to fail to comply with relevant laws, regulations or government guidance with respect to these programs, we could be subject to significant fines or penalties.

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Any of these events could reduce market acceptance of ARIKAYCE, substantially reduce our revenue, increase the costs of operating our business, and cause us significant reputational damage, among other consequences. If we ultimately receive approval for ARIKAYCE in other jurisdictions, we expect to be subject to similar ongoing regulatory oversight by the relevant foreign regulatory authorities.

If we are unable to obtain adequate reimbursement from government or third-party payors for ARIKAYCE or if we are unable to obtain acceptable prices for ARIKAYCE, our prospects for generating revenue and achieving profitability will be materially adversely affected.

Our prospects for generating revenue and achieving profitability depend heavily upon the availability of adequate reimbursement for the use of ARIKAYCE from governmental and other third-party payors, both in the US and in other markets. We expect a substantial majority of ARIKAYCE revenue will come from Medicare reimbursement. Reimbursement by a third-party payor depends 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.

ARIKAYCE's potential addition to or exclusion from the guidelines of the American Thoracic Society and Infection Diseases Society of America may also be a factor in this determination. Obtaining a determination of coverage and reimbursement 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 expect that, during the first six to twelve months that we commercialize ARIKAYCE, the payors will evaluate it for inclusion on formularies, during which time patients will need to rely primarily on the medical exception process to secure coverage. For sales after that time, we may not be able to provide data sufficient to gain a positive coverage and reimbursement determination or we might need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of ARIKAYCE 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 and/or may set a reimbursement rate that is too low to support a profitable sales price for the product. Subsequent approvals of competitive products could result in a detrimental change to the reimbursement of our products. The occurrence of any of these events likely would adversely impact market acceptance and demand for ARIKAYCE, which, in turn, could affect our ability to successfully commercialize ARIKAYCE and adversely impact our business, financial condition, results of operations and prospects and the value of our common stock.

There is a significant focus in the US healthcare industry and elsewhere on drug prices and value, and public and private payors are taking increasingly aggressive steps to control their expenditures for pharmaceuticals by, inter alia, negotiating manufacturer discounts and placing restrictions on reimbursement, and patient access to, medications. These pressures could negatively affect our business. 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. For instance, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) expanded Medicare outpatient prescription drug coverage for the elderly through Part D prescription drug plans sponsored by private entities and authorized such plans to use formularies where they can limit the number of drugs that will be covered in any therapeutic class. The plans generally negotiate significant price concessions as a condition of formulary placement. The MMA also introduced a new reimbursement methodology based on average sales prices for physician-administered drugs, which is generally believed to have resulted in lower Medicare reimbursement for physician-administered drugs. These cost reduction initiatives and other provisions of this legislation provide additional pressure to contain and reduce drug prices and could decrease the coverage and price

that we receive for any approved products and could seriously harm our business. Although the MMA applies only to drug benefits for Medicare beneficiaries, private 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. Additionally, the Patient Protection and Affordable Care Act (ACA) revised the definition of “average manufacturer price” for reporting purposes and increased the minimum percentage for Medicaid drug rebates to states, required drug manufacturers to provide a significant discount (70% as of January 1, 2019) on prescriptions for branded drugs filled while the beneficiary is in the Medicare Part D coverage gap (also known as the donut hole), and imposed

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a significant annual fee on companies that manufacture or import branded prescription drug products. We believe it is likely that the ACA, or any legislation enacted to amend or replace it, will continue the pressure on pharmaceutical pricing, especially under the Medicare program, and also may increase our regulatory burdens and operating costs. Such changes may have a significant impact on our ability to set a product price we believe is fair and may adversely affect our ability to generate revenue and achieve or maintain profitability. We expect further federal and state proposals and health care reforms to continue to be proposed by legislators and/or the US President, which could limit the prices that can be charged for the products we develop or may otherwise limit our commercial opportunity. See Reimbursement of Pharmaceutical Products in Item 1 of Part I of this 10-K for more information. In addition, in connection with various government programs, we are required to report certain pricing information to the government, and the failure to do so may subject us to penalties.

Payors may also restrict coverage of some products, particularly those for higher-priced drugs such as ARIKAYCE, by using a variable co-payment structure that imposes higher costs on patients for drugs that are not preferred by the payor and by imposing requirements for prior authorization or step edits.

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

We have had discussions with third-party payors regarding our price for ARIKAYCE, but our pricing may meet resistance from them and the public generally. If we are unable to obtain adequate reimbursement of ARIKAYCE, the adoption of ARIKAYCE by physicians and patients may be limited. This, in turn, could affect our ability to successfully commercialize ARIKAYCE and adversely impact our business, financial condition, results of operations and prospects and the value of our common stock.

ARIKAYCE could develop unexpected safety or efficacy concerns, which would likely have a material adverse effect on us.

ARIKAYCE was granted accelerated approval from the FDA based on Month 6 data from the CONVERT study. In the US, ARIKAYCE will now be used by larger numbers of patients, potentially for longer periods of time, and we and others (including regulatory agencies and private payors) will collect extensive information on the efficacy and safety of ARIKAYCE by monitoring its use in the marketplace. In addition, we will conduct a confirmatory trial to assess and describe the clinical benefit of ARIKAYCE in patients with MAC lung disease and may conduct additional trials in connection with lifecycle management programs for ARIKAYCE in the US. New safety or efficacy data from both market surveillance and our clinical trials may result in negative consequences including the following:

- Modification to product labeling or promotional statements, such as additional boxed or other warnings or contraindications, or the issuance of additional "Dear Doctor Letters" or similar communications to healthcare professionals;
- Required changes in the administration of ARIKAYCE;
- Imposition of additional post-marketing surveillance, post-marketing clinical trial requirements, distribution restrictions or other risk management measures, such as a risk evaluation and mitigation strategy (REMS) or a REMS with elements to assure safe use;
- Suspension or withdrawal of regulatory approval;
- Suspension or termination of ongoing clinical trials or refusal by regulators to approve pending marketing applications or supplements to approved applications;
- Suspension of, or imposition of restrictions on, our operations, including costly new manufacturing requirements with respect to ARIKAYCE; and
- Voluntary or mandatory product recalls or withdrawals from the market and costly product liability claims.

Any of these circumstances could reduce ARIKAYCE's market acceptance and would be likely to materially adversely affect our business.

If estimates of the size of the potential markets for ARIKAYCE are overstated or data we have used to identify physicians is inaccurate, our ability to earn revenue to support our business could be materially adversely affected.

We have relied on our 2017 analysis of external sources, including market research funded by us and third parties, and

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internal analyses and calculations to estimate the potential market opportunities for MAC lung disease in the US, where ARIKAYCE has obtained regulatory approval, as well as future jurisdictions in which we may seek approval, including the EU5 (comprised of France, Germany, Italy, Spain and the United Kingdom) and Japan. The externally sourced information used to develop these estimates has been obtained from sources we believe to be reliable, but we have not verified the data from such sources, and their accuracy and completeness cannot be assured. Similarly, our internal analyses and calculations are based upon management's understanding and assessment of numerous inputs and market conditions, including, but not limited to, the projected increase in prevalence of MAC lung disease, Medicare patient population growth and ongoing population shifts to geographies with increased rates of MAC lung disease. These understandings and assessments necessarily require assumptions subject to significant judgment and may prove to be inaccurate. As a result, our estimates of the size of these potential markets for ARIKAYCE could prove to be overstated, perhaps materially.

In addition, we are relying on third-party data to identify the physicians who treat the majority of MAC lung disease patients in the US and to determine how to deploy our resources to market to those physicians; however, we may not be marketing to the appropriate physicians and may therefore be limiting our market opportunity.

We may develop estimates with respect to market opportunities for product candidates in the future, and such estimates would be subject to similar risks. In addition, a potential market opportunity could be reduced if a regulator limits the proposed treatment population for one of our product candidates, similar to the limited population for which ARIKAYCE was approved. In either circumstance, even if we obtain regulatory approval, we may be unable to commercialize the product on a scale sufficient to generate significant revenue, which could have a material adverse effect on our business, financial condition, results of operations and prospects and the value of our common stock.

We currently are building our marketing and sales organization, and we have limited experience as a company in marketing drug products. If we are unable to successfully market and sell ARIKAYCE, our ability to generate revenue will be adversely affected.

In order to commercialize ARIKAYCE, we must develop marketing, market access, sales and distribution capabilities on our own or make arrangements with third parties for its marketing, sale and distribution. We have commenced commercialization of ARIKAYCE in the US, but we may not be successful in these efforts. The establishment and development of our own sales force is and will continue to be expensive and time-consuming. As a result, we may seek one or more partners to handle some or all of the sales and marketing of ARIKAYCE in certain markets outside the US following approval by the relevant regulatory authority in those markets. However, we may not be able to enter into arrangements with third parties to sell ARIKAYCE on favorable terms or at all. In the event that either our own marketing, market access, and sales force or third-party marketing, market access, and sales organizations are not effective, we would not be able to successfully commercialize ARIKAYCE, which would adversely affect our ability to generate revenue and materially harm us.

ARIKAYCE was approved for treatment in a limited population of patients with refractory MAC lung disease, and additional clinical studies and regulatory applications will be required to expand its indication. We may not be successful in these trials or in obtaining such regulatory approval, which may materially adversely affect our prospects and the value of our common stock.

The FDA granted accelerated approval of ARIKAYCE for the treatment of refractory MAC lung disease as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options. Our CONVERT study and 312 study focused on this refractory population, and we do not anticipate obtaining an indication for a broader population of patients with MAC lung disease or any other illnesses or infections without additional clinical data. Additional clinical trials will require additional time and expense. We expect to conduct our confirmatory clinical trial for full approval of ARIKAYCE in the broader population of patients with MAC lung disease, but this trial, along with any other clinical trials of ARIKAYCE may not be successful. Additional results from ongoing and recently completed studies may affect the FDA's benefit-risk analysis for the product. If we are unable to expand the indication for use of ARIKAYCE, our prospects and the value of our common stock may be materially adversely affected.

Risks Related to the Development and Regulatory Approval of Our Product Candidates Generally

Pharmaceutical research and development is very costly and highly uncertain, and we may not succeed in developing product candidates in the future.

Product development in the pharmaceutical industry is an expensive, high-risk, lengthy, complicated, resource intensive process. In order to develop a product successfully, we must, among other things:

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- Identify potential product candidates;
- Submit for and receive regulatory approval to perform clinical trials;
- Design and conduct appropriate preclinical and clinical trials, including confirmatory clinical trials, according to good laboratory practices and good clinical practices and disease-specific expectations of the FDA and other regulatory bodies;
- Select and recruit clinical investigators and subjects for our clinical trials;
- Obtain and correctly interpret data establishing adequate safety of our product candidates and demonstrating with statistical significance that our product candidates are effective for their proposed indications, as indicated by satisfaction of pre-established endpoints;
- Submit for and receive regulatory approvals for marketing; and
- Manufacture the product candidates and device components according to cGMP and other applicable standards and regulations.

There is a high rate of failure inherent in this process, and potential products that appear promising at early stages of development may fail for a number of reasons. Importantly, positive results from preclinical studies of a product candidate may not be predictive of similar results in human clinical trials, and promising results from earlier clinical trials of a product 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 positive results in earlier stages of development and have abandoned development efforts or sought partnerships in order to continue development.

In addition, there are many other difficulties and uncertainties inherent in pharmaceutical research and development that could significantly delay or otherwise materially impair our ability to develop future product candidates, including the following:

- Conditions imposed by regulators, ethics committees or institutional review boards for preclinical testing and clinical trials relating to the scope or design of our clinical trials, including selection of endpoints and number of required patients or clinical sites;
- Challenges in designing our clinical trials to support potential claims of superiority over current standard of care or future competitive therapies;
- Restrictions placed upon, or other difficulties with respect to, clinical trials and clinical trial sites, including with respect to potential clinical holds or suspension or termination of clinical trials due to, among other things, potential safety or ethical concerns or noncompliance with regulatory requirements;
- Delayed or reduced enrollment in clinical trials, or high discontinuation rates;
- Failure by third-party contractors, contract research organizations (CROs), clinical investigators, clinical laboratories, or suppliers to comply with regulatory requirements or meet their contractual obligations in a timely manner;
- Greater than anticipated cost of our clinical trials; and
- Insufficient product supply or inadequate product quality.

Failure to successfully develop future product candidates for any of these reasons may materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

We may not be able to obtain regulatory approvals for ARIKAYCE outside of the US or for our product candidates in the US, Europe, Japan or other markets. Any such failure to obtain regulatory approvals may materially adversely affect us.

We are required to obtain various regulatory approvals prior to studying our products in humans and then again before we market and distribute our products, and the failure to obtain such approvals will prevent us from commercializing our products, which would materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock. While we have obtained accelerated approval for ARIKAYCE in the US, seeking approval for ARIKAYCE in other jurisdictions as well as approval for our product candidates in the US and foreign markets presents significant obstacles. Approval processes in the US, Europe and Japan require the

submission of extensive preclinical and clinical data, manufacturing and quality information regarding the process and facility, scientific data characterizing our product and other supporting data in order to establish safety and effectiveness. These processes are complex, lengthy, expensive, resource intensive and uncertain. Regulators will also conduct a rigorous review of any trade name we intend to use for our products. Even after they approve a trade name, these regulators may request that we adopt an alternative name for the product if adverse event reports indicate a potential for confusion with other trade names and medication error. If we are required to adopt an alternative name, potential commercialization of ARIKAYCE or our product candidates could be delayed or interrupted. We have limited experience in submitting and pursuing applications necessary to obtain these regulatory approvals.

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Data submitted to regulators are subject to varying interpretations that could delay, limit or prevent regulatory agency approval. Even if we believe our clinical trial results are promising, regulators may disagree with our interpretation of data, study design or execution and may refuse to accept our application for review or decline to grant approval. For example, in the fourth quarter of 2014, we filed a marketing authorization application (MAA) with the European Medicines Agency (EMA) for ARIKAYCE as a treatment for, among other things, MAC lung disease in adult patients. The filing was based in part on data from our phase 2 study in patients with refractory MAC lung disease. We subsequently withdrew our MAA after the Committee for Medicinal Products for Human Use concluded that the data submitted did not provide enough evidence to support an approval.

In addition, the grant of a designation by the FDA or approval by the FDA does not ensure a similar decision by the regulatory authorities of other countries, and a decision by one foreign regulatory authority does not ensure regulatory authorities in other foreign countries or the FDA will agree with the decision. For instance, although ARIKAYCE received orphan drug designation in the US, ARIKAYCE did not qualify for orphan drug designation in Japan due to the estimated number of NTM patients in Japan exceeding 50,000. Similarly, clinical studies conducted in one country may not be accepted by regulatory authorities in other countries. Approval procedures vary among countries and can involve additional product testing, including additional preclinical studies or clinical trials, and administrative review periods. The time required to obtain approval in these other territories might differ from that required to obtain FDA approval. We may never obtain approval for ARIKAYCE outside of the US or for our product candidates in the US or other jurisdictions, which would limit our market opportunities and materially adversely affect our business. Even if a product candidate is approved, regulators may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval.

We are currently assessing regulatory strategies which could expedite the development and regulatory review of INS1007 in the US and the EU, but we may be unsuccessful in pursuing such strategies. The FDA has denied our request for orphan drug designation for INS1007 in on-cystic fibrosis (non-CF) bronchiectasis. In addition, although we believe that INS1009 could be eligible for approval under Section 505(b)(2), and thus could rely at least in part on studies not conducted by or for us and for which we do not have a right of reference, we may not obtain approval from the FDA to use this pathway.

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. Resolving such delays could force us or third parties to incur significant costs, limit our allowed activities or the allowed activities of third parties, diminish any competitive advantages that we or our third parties may attain or adversely affect our ability to receive royalties, any of which could materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

For ARIKAYCE to be commercialized in a given market, in addition to regulatory approvals required for ARIKAYCE, the Lamira Nebulizer System must satisfy certain regulatory requirements and its use as a delivery system for ARIKAYCE must be approved or cleared by regulators.

ARIKAYCE is administered using the Lamira Nebulizer System, and the Lamira Nebulizer System must receive regulatory approval or clearance on its own or in conjunction with ARIKAYCE as a combination product in order for us to develop and commercialize ARIKAYCE in a given market. The FDA granted accelerated approval of the Lamira Nebulizer System with ARIKAYCE as part of the approval of the drug/device combination product, and the Lamira Nebulizer System is CE marked by PARI in the EU. However, outside the US and EU, the Lamira Nebulizer System is labeled as investigational for use in our clinical trials, including in Japan, Canada and Australia, and is not approved for commercial use in Japan, Canada or certain other markets in which we may seek to commercialize ARIKAYCE in the future.

If we seek regulatory approval in markets in which the Lamira Nebulizer System is not approved and we and PARI are not successful in obtaining approval for the Lamira Nebulizer System, our ability to commercialize ARIKAYCE

in those markets would be materially impaired. In addition, failure to maintain regulatory approval or clearance of the Lamira Nebulizer System could result in increased development costs, withdrawal of regulatory approval, and delays in ARIKAYCE reaching the market. Failure to obtain or maintain regulatory approval or clearance of the Lamira Nebulizer System could result in potential loss of regulatory approval or otherwise materially harm our business.

We have limited experience conducting and managing the preclinical development activities and clinical trials necessary to obtain regulatory approvals, and we may not succeed in doing so in the future.

ARIKAYCE is our first approved product candidate since our merger with Transave, and we have limited experience in conducting and managing the preclinical development activities and clinical trials necessary to obtain regulatory approvals,

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including approval by the FDA, EMA, Ministry of Health, Labour and Welfare (MHLW), and Pharmaceuticals and Medical Devices Agency (PMDA), which might prevent us from successfully designing, implementing, or completing the clinical trials required to support regulatory approval of our product candidates. The application processes for the FDA, MHLW, PMDA, EMA and other regulatory agencies are complex and difficult and vary by regulatory agency, and we might not be able to demonstrate that our product candidates meet the appropriate standards for regulatory approval or commercialize our product candidates in the US or elsewhere, or commercialize ARIKAYCE in jurisdictions outside of the US, or we might be significantly delayed in doing so. In such circumstances, our business, financial condition, results of operations and prospects and the value of our common stock may be materially adversely affected.

If our clinical studies do not produce positive results or our clinical trials are delayed, or if serious side effects are identified during drug development, we may experience delays, incur additional costs and ultimately be unable to commercialize our product candidates in the US, Europe, Japan or other markets.

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. If we experience delays in our clinical trials or other testing or the results of these trials or tests are not positive or are only modestly positive, including with respect to safety, we may:

- Experience increased product development costs;
- Be delayed in obtaining, or be unable to obtain, regulatory approval for one or more of our product candidates;
- Obtain approval for indications or patient populations that are not as broad as intended or entirely different than those indications for which we sought approval or with labeling with boxed warnings or other warnings or contraindications;
- Need to change the way the product is administered;
- Be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- Have regulatory authorities withdraw, or suspend, their approval of the product or impose risk mitigation strategies such as restrictions on distribution or other REMS;
- Face a shortened patent protection period during which we may have the exclusive right to commercialize our products;
- Have competitors that are able to bring similar products to market before us;
- Be sued for alleged injuries caused to patients using our products or
- Suffer reputational damage.

Such circumstances would impair our ability to commercialize our products and harm our business and results of operations.

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

The completion rate of our clinical trials 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 trial;
- Patient willingness to participate in the trial;

- Discontinuation rates; and
- Competition from other companies' potential clinical trials for the same patient population.

Delays in patient enrollment for our clinical trials, including in the confirmatory clinical trial for ARIKAYCE and the WILLOW study, our global phase 2 study of INS1007 in non-CF bronchiectasis that currently is enrolling patients, like those we encountered in enrolling the CONVERT study, could increase costs and delay commercialization and sales, if any, of our products. Once enrolled, patients may elect to discontinue participation in a clinical trial at any time. If patients elect to discontinue participation in our clinical trials at a higher rate than expected, we may be unable to generate the data required by regulators for approval of our product candidates.

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Risks Related to Our Reliance on Third Parties

We rely on third parties including collaborators, CROs, clinical and analytical laboratories, contract manufacturing organizations (CMOs) and other providers for many services that are critical to our business. If we are unable to form and sustain these relationships, or if any third-party arrangements that we may enter into are unsuccessful, including due to non-compliance by such third parties with our agreements or applicable law, our ability to develop and commercialize our products may be materially adversely affected.

We currently rely, and expect to continue to rely, on third parties for significant research, analytical services, preclinical development, clinical development and manufacturing of our product candidates and commercial scale manufacturing of ARIKAYCE and the Lamira Nebulizer System. For example, we do not own facilities for clinical-scale or commercial manufacturing of our product candidates, and we currently rely on Therapure Biopharma Inc. (Therapure) and Ajinimoto Althea, Inc. (Althea) to provide our clinical and commercial supply of ARIKAYCE. Additionally, almost all of our clinical trial work is done by CROs, such as SynteractHCR, Inc., our CRO for both the CONVERT and 312 studies, and clinical laboratories. Reliance on these third parties poses a number of risks, including the following:

- The diversion of management time and cost of third-party advisers associated with the negotiation, documentation and implementation of agreements with third parties in the pharmaceutical industry;
- The inability to control whether third parties devote sufficient resources to our programs or products, including with respect to meeting contractual deadlines;
- The inability to control the regulatory and contractual compliance of third parties, including their quality systems, processes and procedures, systems utilized to collect and analyze data, and equipment used to test drug product and/or clinical supplies;
- The inability to establish and implement collaborations or other alternative arrangements on favorable terms;
- Disputes with third parties, including CROs, leading to loss of intellectual property rights, delay or termination of research, development, or commercialization of product candidates or litigation or arbitration;
- Contracts with our collaborators fail to provide sufficient protection of our intellectual property; and
- Difficulty enforcing our contractual rights if one of these third parties fails to perform.

We also rely on third parties to select and enter into agreements with clinical investigators to conduct clinical trials to support approval of our product candidates, and the failure of these third parties to appropriately carry out such evaluation and selection can adversely affect the quality of the data from these studies and, potentially, the approval of our products. In particular, as part of future drug approval submissions to the FDA, we must disclose certain financial interests of investigators who participated in any of the clinical studies being submitted in support of approval, or must certify to the absence of such financial interests. The FDA evaluates the information contained in such disclosures to determine whether disclosed interests may have an impact on the reliability of a study. If the FDA determines that financial interests of any clinical investigator raise serious questions of data integrity, the FDA can institute a data audit, request that we submit further data analyses, conduct additional independent studies to confirm the results of the questioned study, or refuse to use the data from the questioned study as a basis for approval. A finding by the FDA that a financial relationship of an investigator raises serious questions of data integrity could delay or otherwise adversely affect approval of our products.

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

We may not have, or may be unable to obtain, sufficient quantities of ARIKAYCE, the Lamira Nebulizer System or our product candidates to meet our required supply for commercialization or clinical studies, which would materially harm our business.

We do not have any in-house manufacturing capability other than for small-scale pre-clinical development programs and depend completely on a small number of third-party manufacturers and suppliers for the manufacture of our product candidates on a clinical or commercial scale. For instance, we are and expect to remain dependent upon

Therapure, Althea and eventually Patheon to supply ARIKAYCE both for our clinical trials and commercial sale. Althea manufactures ARIKAYCE at a relatively small scale; Therapure, operates at a larger scale than Althea. ARIKAYCE currently has a limited shelf life, and we may not be able to maintain adequate quantities to meet future demand. As additional supporting data become available, we believe the current approved shelf life for product manufactured at our CMOs will increase. If we encounter delays or difficulties in the manufacturing process that disrupt our ability to supply our distributors with ARIKAYCE, we may experience a product stock-out, which would likely have a material adverse effect on our business and reputation. In addition, we have entered into certain agreements with Patheon related to increasing our long-term production capacity for ARIKAYCE commercial inventory, although Patheon's supply obligations will commence only after certain technology transfer and

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construction services are completed. Any delay in the commencement of Patheon's supply obligations, whether due to delays in technology transfer and construction or from adding Patheon to our NDA as a CMO, would increase the risks associated with either Therapure or Althea being unable to provide us with an adequate supply of ARIKAYCE.

We are also dependent upon PARI being able to provide an adequate supply of nebulizers both for commercial sale of ARIKAYCE and any ongoing clinical trials, as PARI is the sole manufacturer of the Lamira Nebulizer System. We have no alternative supplier for the nebulizer, and because significant effort and time were expended in the optimization of the nebulizer for use with ARIKAYCE, we do not intend to seek an alternative or secondary supplier. In the event PARI cannot provide us with sufficient quantities of the nebulizer, replication of the optimized device by another party would likely require considerable time and additional regulatory approval. In the case of certain specified supply failures, we have the right under our commercialization agreement with PARI to make the nebulizer and have it made by certain third parties, but not those deemed under the commercialization agreement to compete with PARI.

We do not have long-term commercial agreements with all of our suppliers and if any of our suppliers are unable or unwilling to perform for any reason, we may not be able to locate suppliers or enter into favorable agreements with them.

An inadequate supply of ARIKAYCE or the Lamira Nebulizer System could harm our commercial efforts or delay or impair clinical trials of ARIKAYCE or our product candidates and adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

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

Manufacturers of ARIKAYCE, the Lamira Nebulizer System and our product candidates are subject to cGMP, Quality System Regulations and similar standards. While we have policies and procedures in place to select third-party manufacturers for our product and product candidates that adhere, and monitor their adherence to, such standards, they may nonetheless fail to do so. Similarly, while we have entered into a Commercialization Agreement with PARI for the manufacture of the Lamira Nebulizer System for use with ARIKAYCE, PARI may fail to adhere to applicable standards. These manufacturers and their facilities will be subject to periodic review and inspections by the FDA and other regulatory authorities following regulatory approval of our products, as with ARIKAYCE. For instance, to monitor compliance with applicable regulations, the FDA routinely conducts inspections of facilities and may identify potential deficiencies. The FDA issues what are referred to as "FDA Form 483s" that set forth observations and concerns identified during its inspections. Failure to satisfactorily address the concerns or potential deficiencies identified in a Form 483 could result in the issuance of a warning letter, which is a notice of the issues that the FDA believes to be significant regulatory violations requiring prompt corrective actions. Failure to respond adequately to a warning letter, or to otherwise fail to comply with applicable regulatory requirements could result in enforcement, remedial and/or punitive actions by the FDA or other regulatory authorities.

If one of these manufacturers fails to maintain compliance with regulatory requirements or experiences supply problems, including in the scale-up of commercial production, the production of ARIKAYCE, the Lamira Nebulizer System and our product candidates could be interrupted, resulting in delays, additional costs or restrictions on the marketing or sale of our products. An alternative manufacturer would need to be qualified, through regulatory filings, which could result in further delay. The regulatory authorities may also require additional testing if a new manufacturer is relied upon for commercial production. In addition, with respect to our product candidates, our manufacturers and their facilities are subject to pre-approval cGMP inspection by the FDA and other regulatory authorities, and the findings of the cGMP inspection could result in a failure to obtain, or a delay in obtaining, regulatory approval for future product candidates.

Risks Related to the Operation of our Business

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 and the value of our common stock.

We depend heavily on our management team and our principal clinical and commercial personnel, the loss of whose services might significantly delay or prevent the achievement of our research, development or commercialization objectives. Our success depends, in large part, on our ability to attract and retain qualified management, clinical and commercial personnel, and on our ability to develop and maintain important relationships with commercial partners, leading research institutions and key distributors.

Competition for skilled personnel in our industry and market is intense because of the numerous pharmaceutical and

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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 clinical and commercial personnel from universities, research institutions, and other third parties. We cannot assure that we will attract and retain such persons or maintain such relationships. Our inability to retain and attract qualified employees would materially harm our business, financial condition, results of operations and prospects and the value of our common stock.

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

In connection with our commercial launch of ARIKAYCE and international expansion, we expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs, quality, commercial compliance, medical affairs, and sales and marketing. For example, we plan to hire additional personnel in connection with our commercial launch of ARIKAYCE and preparation for potential regulatory filings for ARIKAYCE in other markets. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to the limited experience of our management team in managing a company with this anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The physical expansion of our operations may lead to significant costs and may divert our management and business development resources. We may not be able to effectively manage the expansion of our operations, which could delay the execution of our business plans or disrupt our operations.

Any acquisitions we make, or collaborative relationships we enter into, may not be clinically or commercially successful, and may require financing or a significant amount of our available cash, which could adversely affect our business.

As part of our business strategy, we may effect acquisitions to obtain additional businesses, products, technologies, capabilities and personnel. Acquisitions involve a number of operational risks, including:

- Failure to achieve expected synergies;
- Difficulty and expense of assimilating the operations, technology and personnel of any acquired business;
- The inability to retain the management, key personnel and other employees of any acquired business;
- The inability to maintain any acquired company’s relationship with key third parties, such as alliance partners;
- Exposure to legal claims for activities of any acquired business prior to acquisition;
- Diversion of our management’s attention from our core business; and
- Potential impairment of intangible assets, adversely affecting our reported results of operations and financial condition.

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

If we make one or more significant acquisitions or enter into a significant collaboration in which the consideration includes cash, we may be required to use a substantial portion of our available cash and/or need to raise additional capital, which could adversely affect our financial condition.

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, particularly as we now commercialize ARIKAYCE in the US. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for ARIKAYCE and any other products that we may commercialize, and a corresponding loss of revenue

- substantial monetary awards to patients or trial participants;
- significant time and costs to defend the related litigation
- withdrawal or reduced enrollment of clinical trial participants; and
- reputational harm and significant negative media attention.

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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 and prospects and the value of our common stock.

Our business and operations, including our drug development programs, could be materially disrupted in the event of system failures, security breaches, violations of data protection laws or data loss or damage by us or our CROs or other contractors or consultants.

Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If such an event were to occur and cause interruptions in our operations, it could have a material adverse effect on our business operations, including a material disruption of our drug development and commercialization programs. Unauthorized disclosure of sensitive or confidential patient or employee data, including personally identifiable information, whether through breach of computer systems, systems failure, employee negligence, fraud or misappropriation, or otherwise, or unauthorized access to or through our information systems and networks, whether by our employees or third parties, could result in negative publicity, legal liability and damage to our reputation. Unauthorized disclosure of personally identifiable information could also expose us to sanctions for violations of data privacy laws and regulations around the world. To the extent that any disruption or security breach resulted in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed. For example, the loss of or damage to clinical trial data, such as from completed or ongoing clinical trials, for any of our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data.

Although we have general liability insurance coverage, including coverage for errors and omissions, our insurance may not cover all claims, continue to be available on reasonable terms or be sufficient in amount to cover one or more large claims; additionally, the insurer may disclaim coverage as to any claim. The successful assertion of one or more large claims against us that exceed or are not covered by our insurance coverage or changes in our insurance policies, including premium increases or the imposition of large deductible or co-insurance requirements, could have a material adverse effect on our business, financial condition, results of operations and prospects and the value of our common stock.

We have limited experience operating internationally, are subject to a number of risks associated with our international activities and operations and may not be successful in our efforts to expand internationally.

We currently have limited operations outside of the US. As of December 31, 2018, we had 28 employees located in Europe and 6 employees located in Japan, although we have clinical trial sites and suppliers located around the world. In order to meet our long-term goals, we expect to grow our international operations over the next several years, including in Europe and Japan, and continue to source material used in the manufacture of our product candidates from abroad. Consequently, we are and will continue to be subject to risks related to operating in foreign countries, including:

- Limited experience with international regulatory requirements;
- An inability to achieve optimal pricing and reimbursement for ARIKAYCE, if approved in another jurisdiction, or subsequent changes in reimbursement, pricing and other regulatory requirements;

- Any implementation of, or changes to, tariffs, trade barriers and other import-export regulations in the US or other countries in which we, or our third-party partners, operate;
- Unexpected adverse events related to ARIKAYCE or our product candidates occurring in foreign markets that we have not experienced in the US;
- Economic and political conditions, including geopolitical events, such as war and terrorism, foreign currency fluctuations and inflation, which could result in reduced revenue, increased or unpredictable operating expenses and other obligations incident to doing business in, or with a company located in, another country;
- Changes resulting from the UK's vote to exit the EU, including: (i) the uncertainty and instability in economic and market conditions; (ii) the uncertainty regarding the UK’s access to the EU Single Market and the impact on the wider trading, legal, regulatory and labor environments; and (iii) the uncertainty in the European regulatory framework, including the relocation of the EMA from the UK to the Netherlands, and the subsequent potential disruption and delay of EMA regulatory actions; and
- Compliance with foreign or US laws, rules and regulations, including data privacy requirements, labor relations laws,

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tax laws, anti-competition regulations, import, export and trade restrictions, anti-bribery/anti-corruption laws, regulations or rules, which could lead to actions by us or our licensees, distributors, manufacturers, other third parties who act on our behalf or with whom we do business in foreign countries or our employees who are working abroad that could subject us to investigation or prosecution under such foreign or US laws.

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

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. 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. Compounds, products or processes that we develop may become obsolete before we recover any expenses incurred in connection with their development. We face substantial competition from pharmaceutical, biotechnology and other companies, universities and research institutions with respect to nontuberculous mycobacteria (NTM) lung disease, bronchiectasis, and pulmonary arterial hypertension (PAH). Relative to us, most of these entities have substantially greater capital resources, research and development staffs, facilities and experience in conducting clinical studies, obtaining regulatory approvals, and manufacturing and marketing pharmaceutical products. Many of our competitors may achieve product commercialization or obtain patent protection earlier than us. Furthermore, we believe that our competitors have used, and may continue to use, litigation to gain a competitive advantage. Our competitors may also use different technologies or approaches to develop products similar to ARIKAYCE and our product candidates.

We expect that competing successfully will depend, among other things, on 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, as well as product efficacy, safety, reliability, availability, timing and scope of regulatory approval and price. We expect competition to increase as technological advances are made and commercial applications broaden. There are potential competitive products, both approved and in development, which include oral, systemic, or inhaled antibiotic products to treat chronic respiratory infections. For instance, certain entities have expressed interest in studying their products for NTM lung disease and are seeking to advance studies in NTM lung disease caused by mycobacterial species other than MAC; however, we are not aware of any entities currently conducting clinical trials for the treatment of refractory MAC lung disease or of any other approved inhaled therapies specifically indicated for NTM lung disease in North America, Europe or Japan. If any of our competitors develops a product that is more effective, safe, tolerable or, convenient or less expensive than ARIKAYCE or our product candidates, it would likely materially adversely affect our ability to generate revenue. 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 or other countries where we may sell ARIKAYCE. In addition, in an effort to put downward pressure on drug pricing, Congress and the FDA are working to facilitate generic competition, which could result in our experiencing competition earlier than otherwise would be the case.

There are also other amikacin products that have been approved by the FDA, MHLW and other regulatory agencies for use in other indications, and physicians may elect to prescribe those products rather than ARIKAYCE to treat the indications for which ARIKAYCE has received approval, which is commonly referred to as off-label use. Although regulations prohibit a drug company from promoting off-label use of its product, the FDA and other regulatory agencies do not regulate the practice of medicine and cannot direct physicians as to what product to prescribe to their patients. As a result, we would have limited ability to prevent any off-label use of a competitor’s product to treat diseases for which we have received FDA or other regulatory agency approval, even if this use violates our patents or any statutory exclusivities that the FDA may grant for the use of amikacin to treat such diseases. If we are unable to compete successfully, it will materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

Risks Related to Our Intellectual Property

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

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain and involves complex legal, technical, scientific and factual questions, and our success depends in large part on our ability to protect our proprietary technology and to obtain and maintain patent protection for our products, prevent third parties from infringing our patents, both domestically and internationally. We have sought to protect our proprietary position by filing patent applications in the US and abroad related to our novel technologies and products that are important to our business. This process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a

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reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Our existing patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technologies or from developing competing products and technologies.

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

Additionally, patents issued to us or our licensors may be challenged, narrowed, invalidated, held to be unenforceable or circumvented through litigation, which could limit our ability to stop competitors from marketing similar products or reduce the term of patent protection for amikacin liposome inhalation suspension or our product candidates. US patents and patent applications may also be subject to interference or derivation proceedings, and US patents may be subject to re-examination proceedings, reissue, post-grant review and/or *inter partes* review in the USPTO. Our foreign patents have been and may be in the future subject to opposition or comparable proceedings in the corresponding foreign patent office, which could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. See *Intellectual Property - ARIKAYCE Patents and Trade Secrets* in Item 1 of Part I of this 10-K for more information on our European patents that have been previously opposed.

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

If we are not able to adequately prevent disclosure of trade secrets and other proprietary information, the value of ARIKAYCE and our product candidates could be materially 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. Regulators also may disclose information we consider to be proprietary to third parties under certain circumstances, including in response to third-party requests for such disclosure under the Freedom of Information Act or comparable laws. Additionally, the FDA, as part of its Transparency Initiative, continues to consider whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time whether and how the FDA's disclosure policies may change in the future.

We may not be able to enforce our intellectual property rights throughout the world, which could harm our business.

The legal systems of some foreign countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to life sciences. Many companies have encountered significant problems in protecting and defending intellectual property rights in such foreign jurisdictions. For example, certain foreign countries have compulsory licensing laws under which a patent owner may be required to grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no

benefit. This legal environment could make it difficult for us to stop the infringement of our patents or in-licensed patents or the misappropriation of our other intellectual property rights. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, and our efforts to protect our intellectual property rights in such countries may be inadequate.

The drug research and development industry has a history of intellectual property litigation, and we could become involved in costly intellectual property disputes, which could delay or impair our product development efforts or prevent us from, or

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increase the cost of, commercializing ARIKAYCE or any other approved product candidate.

Third parties may claim that we have infringed upon or misappropriated their proprietary rights. Any existing third-party patents, or patents that may later issue to third parties, could negatively affect our commercialization of ARIKAYCE, INS1007, INS1009 or any other product candidate that receives regulatory approval. For instance, PAH is a competitive indication with established products, including other formulations of treprostinil. Our supply of the active pharmaceutical ingredient for INS1009 is dependent upon a single supplier. The supplier owns patents on its manufacturing process, and we have filed patent applications for INS1009; however, a competitor in the PAH indication may claim that we or our supplier have infringed upon or misappropriated its proprietary rights. Moreover, in the event that we pursue approval of INS1009, or any other product candidate, via the 505(b)(2) regulatory pathway, we will be required to file a certification against any unexpired patents listed in the Orange Book for the third-party drug we rely upon as part of our regulatory submission. This certification process may lead to litigation and could also delay launch of a product candidate, if approved by regulators.

In the event of successful litigation or settlement of claims against us for infringement or misappropriation of a third-party's proprietary rights, as in 2007 with respect to IPLEX, we may be required to take actions including but not limited to the following:

- Paying damages, including up to treble damages, royalties, and the other party's attorneys' fees, which may be substantial;
- Ceasing development, manufacture, marketing and sale of products or use of processes that infringe the proprietary rights of others;
- Expending 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, or may result in significant regulatory delays associated with conducting additional clinical trials or other steps to obtain regulatory approval; and/or
- Acquiring one or more licenses from third parties, which may not be available to us on acceptable terms or at all.

We may also have to undertake costly litigation or engage in other proceedings, such as interference or *inter partes* review, to enforce or defend the validity of any patents issued or licensed to us, to confirm the scope and validity of our or a licensor's proprietary rights or to defend against allegations that we have infringed a third-party's intellectual property rights.

Any proceedings regarding our intellectual property rights are likely to be time consuming and may divert management attention from operation of our business, and could have a material adverse effect on our business, financial condition, results of operations and prospects and the value of our common stock.

Certain of the agreements to which we are, or may become, a party relating to ARIKAYCE and our product candidates impose, or may in the future impose, restrictions on our business or other material obligations on us. If we fail to comply with these obligations, our business could be adversely affected, including as a result of the loss of license rights that are important to our business.

We are a party to various agreements related to ARIKAYCE and our product candidates, including licensing agreements with PARI and AstraZeneca, which we view as material to our business. For additional information regarding the terms of these agreements, see *Business - License and Other Agreements* in Item 1 of Part I of this 10-K. These agreements impose a number of obligations on us and our business, including restrictions on our ability to freely develop or commercialize our product candidates and requirements to make milestone and royalty agreements to our counterparties upon certain events. Under our license agreement with AstraZeneca, AstraZeneca retains a right of first negotiation pursuant to which it may exclusively negotiate with us before we can negotiate with a third-party regarding any transaction to develop or commercialize INS1007, subject to certain exceptions. While this right of first negotiation is not triggered by a change of control, it may impede or delay our ability to consummate certain other transactions involving INS1007.

If we fail to comply with our obligations under these agreements, our counterparties may have the right to take action against us, up to and including termination of a relevant license. For instance, under our licensing agreement with PARI, with respect to NTM lung disease and bronchiectasis, we have specific obligations to use commercially

reasonable efforts to achieve certain developmental and regulatory milestones by set deadlines. Additionally, for NTM lung disease, we are obligated to use commercially reasonable efforts to achieve certain commercial milestones in Europe. The consequences of our failing to use commercially reasonable efforts to achieve certain commercial milestones are context-specific, but include ending PARI's non-compete obligation, making the license non-exclusive and terminating the license, in each case with respect to the applicable indication. Similarly, under our license agreement with AstraZeneca, AstraZeneca may terminate our license to INS1007 if we fail to use commercially reasonable efforts to develop and commercialize a product based on INS1007, or we are subject to a bankruptcy or insolvency. Reduction or elimination of our licensed rights may result in our having to negotiate new or reinstated licenses with less favorable terms and may materially harm our business.

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Finally, if we do not proceed with the development of our ARIKAYCE program in the NTM lung disease or CF indications, certain of our contract counterparties may elect to proceed with the development of these indications.

Risks Related to Government Regulation

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

Our industry is highly regulated and changes in or revisions to laws and regulations that make gaining regulatory approval, reimbursement and pricing more difficult or subject to different criteria and standards may adversely impact our business, operations or financial results.

The Administration and the majority party in the Senate have indicated their ongoing desire to repeal the ACA and, in December 2017, Congress repealed the ACA's individual mandate, i.e., the penalty imposed on individuals who do not obtain health care coverage. It is unclear what the effect of this partial repeal will be and whether, when and how repeal of other sections of the law may be effectuated and what the effect on the healthcare sector will be. In December 2018, a federal district court judge in Texas found the ACA to be unconstitutional, although the ruling was stayed while the case is appealed. It is unclear what the outcome of this litigation and other pending challenges to the ACA's constitutionality, as well as the effect of these matters on the healthcare sector, will be. The US President has indicated an interest in taking steps to lower drug prices, such as having the federal government negotiate drug prices with pharmaceutical manufacturers and/or in indexing certain federally reimbursement payments to international drug prices. See *Reimbursement of Pharmaceutical Products* in Item 1 of Part I of this 10-K for more information. Changes to the ACA, to the Medicare or Medicaid programs, or to the ability of the federal government to negotiate or otherwise affect drug prices, or other federal legislation regarding healthcare access, financing or legislation in individual states, could affect our business, financial condition, results of operations and prospects and the value of our common stock. It remains unclear how any new legislation or regulation might affect the prices we may obtain for ARIKAYCE or any of our product candidates for which regulatory approval is obtained.

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, results of operations and prospects and the value of our common stock.

In the US, we are subject to various federal and state health care "fraud and abuse" laws, including anti kickback laws, false claims laws and other laws intended to reduce fraud and abuse in federal and state health care programs. Although we seek to structure our business arrangements in compliance with all applicable requirements, these laws are broadly written, and it is often difficult to determine precisely how the law will be applied in specific circumstances. Accordingly, it is possible that our practices may be challenged under these laws. Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including fines or exclusion or suspension from federal and state health care programs such as Medicare and Medicaid and debarment from contracting with the US government, and our business, financial condition, results of operations and prospects and the value of our common stock may be adversely affected. Our reputation could also suffer. In addition, private individuals have the ability to bring actions on behalf of the government under the federal False Claims Act as well as under the false claims laws of several states.

Under the ACA, we are required to report information on payments or transfers of value to US physicians and teaching hospitals as well as investment interests held by physicians and their immediate family members, which is posted in searchable form on a public website. Failure to submit required information may result in civil monetary penalties.

Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. In addition to the federal government, some states, as well as other countries, including France, require the disclosure of certain payments to health care professionals. The federal privacy regulations under HIPAA, state, and foreign medical record privacy laws may limit access to information identifying those individuals who may be prospective users. 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.

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

Our operations are subject to anti-corruption laws, including the US Foreign Corrupt Practices Act (FCPA), the UK

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Bribery Act and other anti-corruption laws that apply in countries where we do business. The FCPA, UK Bribery Act and these other laws generally prohibit us, our employees and our intermediaries from making prohibited payments to government officials or other persons to obtain or retain business or gain some other business advantage. The CONVERT study includes more than 125 sites in 18 countries, and we conducted the 312 study and plan to conduct the WILLOW study, our global phase 2 study of INS1007 in non-CF bronchiectasis, at a broad range of trial sites around the world. Certain of these jurisdictions pose a risk of potential FCPA violations, and we have relationships with third parties whose actions could potentially subject us to liability under the FCPA or local anti-corruption laws. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

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

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

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 ODA, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition. The company that obtains the first regulatory approval from the FDA for a designated orphan drug for a rare disease generally receives marketing exclusivity for use of that drug for the designated condition for a period of seven years. Similar laws exist in the EU with a term of ten years. See *Business - Government Regulation - Orphan Drug Designation* in Item 1 of Part I of this 10-K for additional information. If a competitor obtains approval of the same drug for the same indication or disease before us, and the FDA grants such orphan drug exclusivity, 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, even if we obtain orphan exclusivity, the FDA may approve another product during our orphan exclusivity period for the same indication under certain circumstances.

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

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our research and development program and manufacturing activities for ARIKAYCE and our product candidates involve the controlled use of hazardous materials and chemicals. We generally contract with third parties for the disposal of these materials and wastes. Although we strive to comply with all pertinent regulations, the risk of environmental contamination, damage to facilities or injury to personnel from the accidental or improper use or control of these materials remains. In addition to any liability we could have for any misuse by us of hazardous materials and chemicals, we could also potentially be liable for activities of our CMOs or other third parties. Any such liability, or even allegations of such liability, could materially adversely affect our results of operations and financial condition. We also could incur significant costs as a result of civil or criminal fines and penalties.

In addition, we may incur substantial costs 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.

Risks Related to Our Financial Condition and Need for Additional Capital

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

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We have incurred losses each previous year of our operation, except in 2009, when we sold our manufacturing facility and certain other assets to Merck, and we did not generate significant revenue during the years ended December 31, 2018, 2017 or 2016. As of December 31, 2018, our accumulated deficit was $1,282.2 million. For the years ended December 31, 2018, 2017 and 2016, our consolidated net loss was $324.3 million, $192.6 million and $176.3 million, respectively. Our ability to generate revenue will depend on the success of commercial sales of ARIKAYCE; however, we do not anticipate our revenue from the sale of ARIKAYCE will be sufficient for us to become profitable without reductions in our operating expenses. Despite our recent launch of ARIKAYCE in the US, we expect to continue to incur substantial operating expenses, and resulting operating losses, for the foreseeable future as we:

- initiate or continue clinical studies of our product candidates;
- initiate a post-marketing clinical trial of ARIKAYCE, as required by the FDA
- seek to discover or in-license additional product candidates
- seek regulatory approvals for ARIKAYCE in foreign markets
- scale-up manufacturing capabilities for future ARIKAYCE production, including the build-out of production capacity at Patheon and process improvements in order to manufacture at a commercial scale and
- enhance operational, compliance, financial, quality and information management systems and hire more personnel, including personnel to support our commercialization efforts and development of our product candidates.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis.

We may need to raise additional funds 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 expend substantial financial resources to commercialize ARIKAYCE, including expenditures on product sales, marketing, manufacturing and distribution, fund the confirmatory post-marketing study and continue research and development of and, where applicable, seek regulatory approval for ARIKAYCE and our product candidates. We may need to raise additional capital to fund these activities, including due to changes in our product development plans or misjudgment of expected costs, to fund corporate development, to maintain our intellectual property portfolio or to resolve litigation. As of December 31, 2018, we had $495.1 million of cash and cash equivalents on hand. Our operating expenses, capital expenditures and long-term investments were significantly higher in 2018 than in 2017, reflecting our investment in the build-out of our commercial organization to support global expansion activities for ARIKAYCE, including the launch of ARIKAYCE in the US in the fourth quarter of 2018, the build-up of third-party manufacturing capacity and manufacture of commercial inventory, which includes capital and long-term investments, and continued investment in research and development as well as selling, general and administrative expenses. We do not know whether additional financing will be available when needed, or, if available, whether the terms will be favorable. If adequate funds are not available to us when needed, we may be forced to delay, restrict or eliminate all or a portion of our development programs or commercialization efforts.

We have outstanding indebtedness in the form of convertible senior notes, and may incur additional indebtedness in the future, which could adversely affect our financial position, prevent us from implementing our strategy, and dilute the ownership interest of our existing shareholders.

In January 2018, we completed an underwritten public offering of 1.75% convertible senior notes due 2025 (the Convertible Notes). The Convertible Notes may be convertible into common stock at an initial conversion rate of 25.5384 shares of common stock per $1,000 principal amount of Convertible Notes. We sold $450.0 million aggregate principal amount of the Convertible Notes, including the exercise in full of the underwriters' option to purchase additional Convertible Notes, resulting in net proceeds of approximately $435.8 million. Holders of the Convertible Notes may convert their Convertible Notes at their option at any time prior to the close of business on the business day immediately preceding October 15, 2024 only under certain circumstances. On or after October 15, 2024 until the close of business on the second scheduled trading day immediately preceding the maturity date, holders may convert

their Convertible Notes at any time. Upon conversion of the Convertible Notes, we may deliver cash, shares of our common stock or a combination of cash and shares of our common stock, at our election.

The degree to which we are leveraged could have negative consequences, such as the following:

- we may be more vulnerable to economic downturns, less able to withstand competitive pressures, and less flexible in responding to changing economic conditions;
- our ability to obtain financing in the future may be limited;

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- a substantial portion of our cash flows from operations in the future may be required for the payment of the principal amount of the Convertible Notes when they or any additional indebtedness become due
- we may elect to make cash payments upon conversion of the Convertible Notes, which would reduce our available cash.

Our ability to pay principal or interest on or, if desired, to refinance our indebtedness, including the Convertible Notes, depends on our future performance, which is subject to economic, financial, competitive and other factors, some of which are beyond our control. Our business may not generate cash flow from operations in the future sufficient to satisfy any obligations under the Convertible Notes to make cash payments to noteholders or our obligations under any future indebtedness we may incur. If we are unable to generate such cash flow, we may be required to delay, restrict or eliminate all or a portion of our development programs or commercialization efforts or refinance or obtain additional equity capital on terms that may be onerous or highly dilutive. If we do not meet our debt obligations, it could materially adversely affect our results of operations, financial condition and the value of our common stock.

The conversion of some or all of the Convertible Notes will dilute the ownership interests of our existing shareholders to the extent we deliver shares upon their conversion. Any sales in the public market of the common stock issuable upon such conversion could adversely affect prevailing market prices of our common stock. In addition, the existence of the Convertible Notes may encourage short selling by market participants because the conversion of the Convertible Notes could be used to satisfy short positions, or anticipated conversion of the Convertible Notes into shares of our common stock could depress the price of our common stock.

The accounting method for the Convertible Notes may have an adverse effect on our reported financial results.

Accounting guidance requires that we separately account for the liability and equity components of the Convertible Notes because they may be settled entirely or partially in cash upon conversion in a manner that reflects our economic interest cost. As a result, the equity component of the Convertible Notes is required to be included in the additional paid-in capital section of shareholders' equity on our consolidated balance sheet, and the value of the equity component is treated as original issue discount for purposes of accounting for the debt component of the Convertible Notes. We may report greater net loss (or lower net income) in our financial results because this guidance requires interest to include both the current period's amortization of the debt discount and the instrument's coupon interest, which could adversely affect our reported or future financial results, the market price of our common stock and the trading price of the Convertible Notes.

Holders may convert their Convertible Notes at their option at any time prior to the close of business on the business day immediately preceding October 15, 2024 only under certain circumstances. For example, holders may convert their Convertible Notes at their option during any quarter commencing after the quarter ending March 31, 2018 (and only during such quarter) if the last reported sale price of our common stock for at least 20 trading days (whether or not consecutive) during a period of 30 consecutive trading days ending on the last trading day of the immediately preceding quarter is greater than or equal to 130% of the conversion price on each applicable trading day. If the Convertible Notes become convertible prior to October 15, 2024, we may be required to reclassify our Convertible Notes and the related debt issuance costs as current liabilities and certain portions of our equity outside of equity to mezzanine equity, which would have an adverse impact on our reported financial results for such quarter, and could have an adverse impact on the market price of our common stock and the trading price of the Convertible Notes.

Intangible assets comprised approximately 10% of our total assets as of December 31, 2018. A reduction in the value of our intangible assets could have a material adverse effect on our results of operations, financial condition and the value of our common stock.

As a result of the merger with Transave in 2010, we recorded an intangible in-process research and development (IPRD) asset of $77.9 million and goodwill of $6.3 million on our balance sheet. As a result of the clinical hold on ARIKAYCE announced in late 2011, we recorded a charge of $26.0 million in the fourth quarter of 2011 that reduced the value of IPRD to $58.2 million and reduced goodwill to zero. In addition, in September 2018 we recorded an additional $1.7 million in intangible assets related to a milestone to PARI as a result of FDA approval of ARIKAYCE. As of December 31, 2018, the balance of these intangibles, net of amortization was $57.0 million and $1.7 million, respectively. Future activities or events could result in additional write-downs of these intangible assets, which could materially adversely affect our results of operations, financial condition and the value of our common stock.

We may be unable to use certain of our net operating losses and other tax assets.

We have substantial tax loss carry forwards for US federal income tax and state income tax purposes, and beginning in

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2015, we had tax loss carry forwards in Ireland as well. In general, our net operating losses and tax credits have been fully offset by a valuation allowance due to uncertainties surrounding our ability to realize these tax benefits. In particular, our ability to fully use certain US tax loss carry forwards and general business tax credit carry forwards recorded prior to December 2010 to offset future income or tax liability is limited under section 382 of the Internal Revenue Code of 1986, as amended (the Code). Changes in the ownership of our stock, including those resulting from the issuance of shares of our common stock offerings or upon exercise of outstanding options, may limit or eliminate our ability to use certain net operating losses and tax credit carry forwards in the future.

Risks Related to Ownership of Our Common Stock

The market price of our stock has been and may continue to be highly volatile, which could lead to shareholder litigation against us.

Our common stock is listed on the Nasdaq Global Select Market under the ticker symbol “INSM”. The market price of our stock has been and may continue to be highly volatile and could be subject to wide fluctuations in price in response to various factors, including those discussed herein, many of which are beyond our control. In addition, the stock market has from time to time experienced extreme price and volume fluctuations, which have particularly affected the market prices for emerging biotechnology and pharmaceutical companies like us, and which have often been unrelated to their operating performance.

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. We previously faced a shareholder suit following a decline in our stock price. If any of our shareholders bring a lawsuit against us in the future, it could have a material adverse effect on our business. We have insurance policies related to some of the risks associated with our business, including directors’ and officers’ liability insurance policies; however, our insurance coverage may not be sufficient and our insurance carriers may not cover all claims in a given litigation. If we are not successful in our defense of claims asserted in shareholder litigation, those claims are not covered by insurance or they exceed our insurance coverage, we may have to pay damage awards, indemnify our executive officers, directors and third parties from damage awards that may be entered against them and pay our and their costs and expenses incurred in defense of, or in any settlement of, such claims. In addition, such shareholder suits could divert the time and attention of management from our business.

Certain provisions of Virginia law, our articles of incorporation and amended and restated bylaws and arrangements between us and our employees 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, our articles of incorporation and amended and restated bylaws and arrangements with our employees 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 or arrangements include:

- The ability to issue preferred stock with rights senior to those of our common stock without any further vote or action by the holders of our common stock. The issuance of preferred stock could decrease the amount of earnings and assets available for distribution to the holders of our common stock or could adversely affect the rights and powers, including voting rights, of the holders of our common stock. In certain circumstances, such issuance could have the effect of decreasing the market price of our common stock.
- The existence of a staggered board of directors in which there are three classes of directors serving staggered three-year terms, thus expanding the time required to change the composition of a majority of directors.
- The requirement that shareholders provide advance notice when nominating director candidates to serve on our Board of Directors.
- The inability of shareholders to convene a shareholders’ meeting without the chairman of the board, the president or a majority of the board of directors first calling the meeting.
- The prohibition against entering into a business combination with the beneficial owner of 10% or more of our outstanding voting stock for a period of three years after the 10% or greater owner first reached that level of stock ownership, unless certain criteria are met.

- In addition to severance agreements with our officers and provisions in our incentive plans that permit acceleration of equity awards upon a change in control, a severance plan for eligible full-time employees that provides such employees with severance equal to six months of their then-current base salaries in connection with a termination of employment without cause upon, or within 18 months following, a change in control.

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We previously had a shareholder rights plan, or "poison pill," 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.

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ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

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ITEM 2. PROPERTIES

We currently lease 56,617 square feet of laboratory and office space in Bridgewater, New Jersey. The initial term of the lease will expire in November 2019. We do not intend to exercise the option to extend the lease beyond the initial term. In September 2018, the Company entered into a new lease for 117,022 square feet of office space for our new corporate headquarters in Bridgewater. We have a one-time option to expand the new leased premises by up to 50,000 square feet prior to the fifth anniversary of the initial lease commencement. The initial term of the new lease will expire in 2030.

We also lease additional laboratory space located in Bridgewater, NJ for which the initial lease term expires in September 2021. In October 2018, the Company expanded this lease to a total of 28,002 square feet. In addition, we lease office space in Ireland, the Netherlands and Japan.

ITEM 3. LEGAL PROCEEDINGS

From time to time, we are a party to various lawsuits, claims and other legal proceedings that arise in the ordinary course of business. While the outcomes of these matters are uncertain, management does not expect that the ultimate costs to resolve these matters will have a material adverse effect on our consolidated financial position, results of operations or cash flows.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

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PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Our trading symbol is "INSM." Our common stock currently trades on the Nasdaq Global Select Market.

On February 15, 2019, the last reported sale price for our common stock on the Nasdaq Global Select Market was $27.07 per share. As of February 15, 2019, there were 137 holders of record of our common stock.

We have never declared or paid cash dividends on our common stock. We anticipate that we will retain all earnings, if any, to support operations and to finance the growth and development of our business for the foreseeable future. Any future determination as to the payment of dividends will be dependent upon these and any contractual or other restrictions to which we may be subject and, to the extent permissible thereunder, will be at the sole discretion of our board of directors and will depend on our financial condition, results of operations, capital requirements and other factors our board of directors deems relevant at that time.

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COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN*
Among Insmed Incorporated, the NASDAQ Composite Index,
the S&P 500 Index, the NASDAQ Pharmaceutical Index and the NASDAQ Biotechnology Index

* $100 invested on 12/31/13 in stock or index, including reinvestment of dividends.
Fiscal year ending December 31.

ITEM 6. SELECTED FINANCIAL DATA

The following selected financial data reflects our consolidated statements of operations and consolidated balance sheets for and as of the years ended December 31, 2018, 2017, 2016, 2015 and 2014. The data below should be read in conjunction with, and is qualified by reference to, *Management's Discussion and Analysis of Financial Condition and Results of Operations* and our consolidated financial statements and notes thereto contained elsewhere in this Annual Report on Form 10-K.

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	Year Ended December 31,				
	2018	2017	2016	2015	2014
	(in thousands, except per share data)				
Statement of Operations Data:					
Revenues	$9,835	$—	$—	$—	$—
Costs and expenses:					
Cost of product revenues (excluding amortization of intangible assets)	2,423	—	—	—	—
Research and development	145,283	109,749	122,721	74,277	56,292
Selling, general and administrative	168,218	79,171	50,679	43,216	31,073
Amortization of intangible assets	1,249	—	—	—	—
Total costs and expenses	317,173	188,920	173,400	117,493	87,365
Operating loss	(307,338)	(188,920)	(173,400)	(117,493)	(87,365)
Investment income	10,341	1,624	604	261	58
Interest expense	(25,472)	(5,925)	(3,498)	(2,889)	(2,415)
Loss on extinguishment of debt	(2,209)	—	—	—	—
Other income (expense), net	602	300	119	(33)	141
Loss before income taxes	(324,076)	(192,921)	(176,175)	(120,154)	(89,581)
Income tax provision (benefit)	201	(272)	98	(1,971)	(10,422)
Net loss	$(324,277)	$(192,649)	$(176,273)	$(118,183)	$(79,159)
Basic and diluted net loss per share	$(4.22)	$(2.89)	$(2.85)	$(2.02)	$(1.84)
Weighted average basic and diluted common shares outstanding	76,889	66,576	61,892	58,633	43,095
Balance Sheet Data:					
Cash and cash equivalents	$495,072	$381,165	$162,591	$282,876	$159,226
Total assets	$604,556	$462,047	$237,956	$356,556	$230,864
Current portion of long-term debt	$—	$—	$—	$3,113	$—
Debt, long-term	$316,558	$55,567	$54,791	$22,027	$24,856
Total shareholders' equity	$208,266	$361,059	$154,483	$311,698	$186,237

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ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

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

EXECUTIVE OVERVIEW

We are a global biopharmaceutical company on a mission to transform the lives of patients with serious and rare diseases. Our first commercial product, ARIKAYCE (amikacin liposome inhalation suspension), received accelerated approval in the United States (US) on September 28, 2018 for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options in a refractory setting as defined by patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. MAC lung disease is a rare and often chronic infection that can cause irreversible lung damage and can be fatal. Our clinical-stage pipeline includes INS1007 and INS1009. INS1007 is a novel oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1) with therapeutic potential in non-cystic fibrosis (non-CF) bronchiectasis and other inflammatory diseases. INS1009 is an inhaled formulation of a treprostinil prodrug that may offer a differentiated product profile for rare pulmonary disorders, including pulmonary arterial hypertension (PAH). We have legal entities in the US, Ireland, Germany, France, the United Kingdom (UK), the Netherlands, Japan and Bermuda.

We have not generated significant revenue since inception, and through December 31, 2018, we had an accumulated deficit of $1,282.2 million. We have financed our operations primarily through the public offerings of our equity securities and debt financings. Although it is difficult to predict our future funding requirements, based upon our current operating plan, we anticipate that our cash and cash equivalents as of December 31, 2018 will enable us to fund our operations for at least the next 12 months.

We expect that over the next few years we will continue to incur losses from operations due to, among other things, research and development expenses in connection with our ongoing and future clinical trials and expenses related to the commercial launch of ARIKAYCE globally, if approved outside the US.

APPROVED PRODUCT - ARIKAYCE

ARIKAYCE is our first approved product. Accelerated approval of ARIKAYCE was supported by preliminary data from our CONVERT study, a global Phase 3 study evaluating the safety and efficacy of ARIKAYCE in adult patients with refractory MAC lung disease, using achievement of sputum culture conversion (defined as three consecutive negative monthly sputum cultures) by Month 6 as the primary endpoint. Patients who achieved sputum culture conversion by Month 6 continued in the CONVERT study for an additional 12 months of treatment following the first monthly negative sputum culture in order to assess the durability of culture conversion, as defined by patients that have completed treatment and continued in the CONVERT study off all therapy for three months. The CONVERT study is ongoing.

Patients who did not culture convert by Month 6 may have been eligible to enroll in our 312 study, an open-label extension study for these non-converting patients who completed six months of treatment in the CONVERT study. The primary objective of the 312 study was to evaluate the long-term safety and tolerability of ARIKAYCE in combination with a standard multi-drug regimen. The secondary endpoints of the 312 study included evaluating the proportion of subjects achieving culture conversion (defined in the same way as the CONVERT study) by Month 6 and the proportion of subjects achieving culture conversion by Month 12, which was the end of treatment. The 312 study has completed.

As a condition of accelerated approval, we must conduct a post-approval confirmatory clinical trial. The required confirmatory trial, which is currently under discussion with the FDA, is proposed to be a randomized, double-blind, placebo-controlled clinical trial to assess and describe the clinical benefit of ARIKAYCE in patients with MAC lung disease. The trial will evaluate the effect of ARIKAYCE on a clinically meaningful endpoint, as compared to an

appropriate control, in the intended patient population of patients with MAC lung disease. Pursuant to the timetable agreed upon with the FDA, the study protocol is expected to be finalized during the first half of 2019, with trial results to be reported by 2024. Continued approval of ARIKAYCE will be contingent upon verification and description of clinical benefit in this study.

PIPELINE PROGRESS

INS1007

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INS1007 is a small molecule, oral, reversible inhibitor of DPP1, which we licensed from AstraZeneca in October 2016. DPP1 is an enzyme responsible for activating neutrophil serine proteases in neutrophils when they are formed in the bone marrow. Neutrophils are the most common type of white blood cell and play an essential role in pathogen destruction and inflammatory mediation. Neutrophils contain the neutrophil serine proteases (including neutrophil elastase, proteinase 3, and cathepsin G) that have been implicated in a variety of inflammatory diseases. In chronic inflammatory lung diseases, neutrophils accumulate in the airways and release active neutrophil serine proteases in excess that cause lung destruction and inflammation. INS1007 may decrease the damaging effects of inflammatory diseases, such as non-CF bronchiectasis, by inhibiting DPP1 and its activation of neutrophil serine proteases. Non-CF bronchiectasis is a progressive pulmonary disorder in which the bronchi become permanently dilated due to chronic inflammation and infection. Currently, there is no cure, and we are not aware of any FDA-approved therapies specifically indicated for non-CF bronchiectasis.

The WILLOW Study

The WILLOW study is a global phase 2, randomized, double-blind, placebo-controlled, parallel group, multi-center clinical study to assess the efficacy, safety and tolerability, and pharmacokinetics of INS1007 administered once daily for 24 weeks in subjects with non-CF bronchiectasis. We commenced enrollment in the WILLOW study in December 2017 and we expect to complete enrollment in mid-2019. In addition, we are exploring the potential of INS1007 in various neutrophil-driven inflammatory conditions.

INS1009

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

Other Development Activities

Our earlier-stage pipeline includes preclinical compounds that we are evaluating in multiple rare diseases of unmet medical need, including gram positive pulmonary infections in CF, NTM lung disease and refractory localized infections involving biofilm. To complement our internal research and development, we actively evaluate in-licensing and acquisition opportunities for a broad range of rare diseases.

KEY COMPONENTS OF OUR RESULTS OF OPERATIONS

Revenues

Product revenues consist primarily of net sales of ARIKAYCE in the US. In October 2018, we began shipping ARIKAYCE to our customers in the US, which include specialty pharmacies and specialty distributors. We recognize revenue for product received by our customers net of allowances for customer credits, including estimated rebates, chargebacks, prompt pay discounts, returns, service fees, and government rebates, such as Medicaid rebates and Medicare Part D coverage gap reimbursements in the US. We also began recognizing revenue from sales to the French National Agency for Medicines and Health Products Safety (ANSM), which granted ARIKAYCE a Temporary Authorizations for Use (Autorisation Temporaire d'Utilisation or ATU).

Cost of product revenues (excluding amortization of intangible assets)

Cost of product revenues (excluding amortization of intangible assets) consist primarily of direct and indirect costs related to the manufacturing of ARIKAYCE sold, including third-party manufacturing costs, packaging services, freight, allocation of overhead costs, and inventory adjustment charges, in addition to royalty expenses due to PARI. We began capitalizing inventory upon FDA approval of ARIKAYCE.

Research and Development (R&D) Expenses

R&D expenses consist of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our research and development functions, including medical affairs. Expenses also include other internal operating

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expenses, the cost of manufacturing our drug candidate(s) for clinical study, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. In addition, our R&D expenses include payments to third parties for the license rights to products in development (prior to marketing approval), such as for INS1007. Our expenses related to manufacturing our drug candidate(s) for clinical study are primarily related to activities at contract manufacturing organizations (CMOs) that manufacture our product candidates for our use, including purchases of active pharmaceutical ingredients. Our expenses related to clinical trials are primarily related to activities at contract research organizations that conduct and manage clinical trials on our behalf.

Since 2011, we have focused our development activities principally on our proprietary, advanced liposomal technology designed specifically for inhaled therapies. Our development efforts in 2018 and 2017 principally related to the development of ARIKAYCE in NTM lung disease.

Selling, General and Administrative (SG&A) Expenses

SG&A expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for our non-employee directors and personnel serving in our executive, finance and accounting, legal and compliance, commercial and pre-commercial, corporate development, field sales, information technology, program management and human resource functions. SG&A expenses also include professional fees for legal services, consulting services, including pre-commercial planning activities such as non-branded disease awareness, insurance, board of director fees, tax and accounting services.

Amortization of Intangible Assets

Upon commercialization of ARIKAYCE, our intangible assets began to be amortized over their estimated useful lives. The fair values assigned to our intangible assets are based on estimates and assumptions we believe are reasonable based on available facts and circumstances. Unanticipated events or circumstances may occur that require us to review the assets for impairment.

Investment Income and Interest Expense

Investment income consists of interest and dividend income earned on our cash and cash equivalents. Interest expense consists primarily of the accretion of debt discount, contractual interest costs and the amortization of debt issuance costs related to our accretion of debt. Debt discount is accreted, and debt issuance costs are amortized, to interest expense using the effective interest rate method over the term of the debt. Our balance sheet reflects debt, net of the debt discount, debt issuance costs paid to the lender, and other third-party costs. Unamortized debt issuance costs associated with extinguished debt are expensed in the period of the extinguishment.

RESULTS OF OPERATIONS

Comparison of the Years Ended December 31, 2018 and 2017

Overview - Operating Results

Our operating results for the year ended December 31, 2018, included the following:

- Total revenues of $9.8 million during the year ended December 31, 2018, as a result of the fourth quarter launch of ARIKAYCE, following US FDA approval on September 28, 2018;
- Cost of product revenues (excluding amortization of intangibles) of $2.4 million during the year ended December 31, 2018 related to sales of ARIKAYCE;
- R&D expenses increased $35.5 million primarily resulting from an increase in external manufacturing expenses and higher compensation and related expenses due to an increase in headcount, as compared to the prior year;
- SG&A expenses increased $89.0 million resulting from higher compensation and related expenses due to an increase in headcount, and an increase in consulting fees relating to pre-commercial planning activities in preparation for the launch of ARIKAYCE, as compared to the prior year;

- Amortization of intangible assets of $1.2 million during the year ended December 31, 2018; and
- Interest expense increased $19.5 million from the issuance of $450.0 million aggregate principal amount of 1.75% convertible senior notes due 2025 (the Convertible Notes) in January 2018.

Net loss for the year ended December 31, 2018 was $324.3 million, or $4.22 per share—basic and diluted, compared with a net loss of $192.6 million, or $2.89 per share—basic and diluted, for the year ended December 31, 2017.

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Revenues

Total revenue consists of net sales of ARIKAYCE, which was approved by the FDA on September 28, 2018 and launched in the US in October 2018. The following table summarizes the sources of revenue for the year ended December 31, 2018 (in thousands):

	For the Year Ended December 31, 2018
Net product revenues, US	$ 9,265
Net product revenues, France ATU	570
Total revenues	$ 9,835

Cost of Product Revenues (excluding amortization of intangibles)

Cost of product revenues (excluding amortization of intangible assets) consist primarily of direct and indirect costs related to the manufacturing of ARIKAYCE sold, including third-party manufacturing costs, packaging services, freight, allocation of overhead costs, and inventory adjustment charges, in addition to royalty expenses due to PARI. We began capitalizing inventory upon FDA approval of ARIKAYCE. Cost of product revenues (excluding amortization of intangible assets) was $2.4 million during the year ended December 31, 2018.

All product costs incurred prior to FDA approval of ARIKAYCE in September 2018 were expensed as R&D expenses. As mentioned above, our cost of product revenues includes certain expenses which are fixed, other expenses that were incurred after FDA approval and royalties based on net sales. We expect our cost of product revenues (excluding amortization of intangible assets), as a percentage of total revenue, to decrease in 2019 as compared to the fourth quarter of 2018.

R&D Expenses

R&D expenses for the years ended December 31, 2018 and 2017 were comprised of the following (in thousands):

	Years Ended December 31,		Increase (decrease)	
	2018	2017	$	%
External Expenses				
Clinical development and research	$30,287	$40,511	$(10,224)	(25.2)%
Manufacturing	43,824	19,808	24,016	121.2%
Regulatory, quality assurance, and medical affairs	12,290	7,308	4,982	68.2%
Subtotal—external expenses	$86,401	$67,627	$18,774	27.8%
Internal Expenses				
Compensation and benefit related expenses	$38,794	$27,689	$11,105	40.1%
Stock-based compensation	9,395	6,491	2,904	44.7%
Other internal operating expenses	10,693	7,942	2,751	34.6%
Subtotal—internal expenses	$58,882	$42,122	$16,760	39.8%
Total	$145,283	$109,749	$35,534	32.4%

R&D expenses increased to $145.3 million during the year ended December 31, 2018 from $109.7 million in the same period in 2017. The $35.5 million increase was primarily due to an increase of $24.0 million in external manufacturing expenses, specifically related to: pre-approval purchases of ARIKAYCE raw materials; pre-approval CMO expenses related to ARIKAYCE commercial inventory production; and construction costs relating to the build-out of a third-party CMO production facility. In addition, there was a $11.1 million increase in compensation and related expenses due to an increase in headcount in the year ended December 31, 2018 as compared to the prior year period. These increases were partially offset by a decrease in clinical development and research expenses related to the CONVERT and 312 clinical trials.

During the year ended December 31, 2018, external R&D expenses of $86.4 million consisted of $69.2 million related to ARIKAYCE, $13.9 million related to INS1007, and $3.3 million related to other research expenses. During the year ended December 31, 2017, external R&D expenses of $67.6 million consisted of $54.6 million related to ARIKAYCE, $10.2 million related to INS1007, and $2.8 million related to other research expenses.

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SG&A Expenses

SG&A expenses for the year ended December 31, 2018 and 2017 were comprised of the following (in thousands):

	Years Ended December 31,		Increase (decrease)	
	2018	2017	$	%
Compensation and benefit related expenses	$62,592	$23,218	$39,374	169.6%
Stock-based compensation	16,845	11,582	5,263	45.4 %
Professional fees and other external expenses	70,248	30,700	39,548	128.8%
Facility related and other internal expenses	18,533	13,671	4,862	35.6 %
Total SG&A expenses	$168,218	$79,171	$89,047	112.5%

SG&A expenses increased to $168.2 million during the year ended December 31, 2018 from $79.2 million in the same period in 2017. The $89.0 million increase was primarily due to $39.4 million in higher compensation and related expenses due to an increase in headcount, including the hiring of our field force, and $39.5 million in professional fees relating to pre-commercial planning activities in preparation for the launch of ARIKAYCE, including non-branded disease awareness, patient support planning, field operations and other consulting fees.

Amortization of Intangible Assets

Amortization of intangible assets for the year ended December 31, 2018 was $1.2 million and is comprised of amortization of acquired ARIKAYCE R&D and amortization of the milestone paid to PARI for the FDA approval of ARIKAYCE.

Interest Expense

Interest expense was $25.5 million for the year ended December 31, 2018 as compared to $5.9 million for 2017. The $19.5 million increase in interest expense in the year ended December 31, 2018 as compared to the prior year period relates to the issuance of $450.0 million aggregate principal amount of Convertible Notes in January 2018. The interest expense on the Convertible Notes is based on an effective interest rate of 7.6%.

Income tax provision (benefit)

The income tax provision (benefit) was $0.2 million and $(0.3) million for the years ended December 31, 2018 and 2017, respectively. The income tax provision for the year ended December 31, 2018 reflects the current income tax expense recorded as a result of taxable income in certain of our subsidiaries in Europe and Japan. The income tax (benefit) for the year ended December 31, 2017 reflects the reversal of the valuation allowance related to alternative minimum tax (AMT) that we paid in 2009 and became refundable as a result of the Tax Act.

On December 22, 2017, the US government enacted comprehensive tax legislation, referred to as the Tax Cuts and Jobs Act (the Tax Act). The Tax Act significantly revised US tax law by, among other provisions, lowering the US federal statutory corporate tax rate from 35% to 21%, imposing a mandatory one-time transition tax on previously deferred foreign earnings, and eliminating or reducing certain income tax deductions. The Tax Act did not have a material impact on our financial statements because our deferred temporary differences are fully offset by a valuation allowance and we did not have any significant offshore earnings from which to record the mandatory transition tax.

Comparison of the Years Ended December 31, 2017 and 2016

Net Loss

Net loss for the year ended December 31, 2017 was $192.6 million, or $2.89 per share—basic and diluted, compared with a net loss of $176.3 million, or $2.85 per share—basic and diluted, for the year ended December 31, 2016. The $16.4 million increase in our net loss for the year ended December 31, 2017 as compared to the same period in 2016 was due to:

- Decreased R&D expenses of $13.0 million primarily resulting from the $30.0 million upfront payment for the license agreement entered into with AstraZeneca for exclusive global rights to INS1007 in October 2016, offset in part by, an increase in expenses related to the WILLOW study and higher compensation and related expenses due to an increase in headcount; and
- Increased SG&A expenses of $28.5 million resulting from an increase in pre-commercial planning activities, including external consulting expenses, and higher compensation and related expenses due to an increase in

headcount.

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In addition, there was a $2.4 million increase in interest expense resulting from the increase in our debt in the second half of 2016.

R&D Expenses

R&D expenses for the years ended December 31, 2017 and 2016 were comprised of the following (in thousands):

	Years Ended December 31,		Increase (decrease)	
	2017	2016	$	%
External Expenses				
Clinical development and research	$40,511	$35,890	$4,621	12.9 %
INS1007 license payment	—	30,000	(30,000)	(100.0)%
Manufacturing	19,808	17,313	2,495	14.4 %
Regulatory, quality assurance, and medical affairs	7,308	4,064	3,244	79.8 %
Subtotal—external expenses	$67,627	$87,267	$(19,640)	(22.5)%
Internal Expenses				
Compensation and benefit related expenses	$27,689	$22,321	$5,368	24.0 %
Stock-based compensation	6,491	6,192	299	4.8 %
Other internal operating expenses	7,942	6,941	1,001	14.4 %
Subtotal—internal expenses	$42,122	$35,454	$6,668	18.8 %
Total	$109,749	$122,721	$(12,972)	(10.6)%

R&D expenses decreased to $109.7 million during the year ended December 31, 2017 from $122.7 million in the same period in 2016. The $13.0 million decrease was due to a $30.0 million upfront payment under the AZ License Agreement related to INS1007 in October 2016 and a $3.7 million decrease in expenses relating to INS1009. These decreases were partially offset by a $10.2 million increase in raw materials purchases and expenses related to the WILLOW trial for INS1007 and a $5.4 million increase in compensation and related expenses due to an increase in headcount. There was also an increase of $3.2 million due to increased regulatory, quality assurance and medical affairs consulting expenses and medical grants.

SG&A Expenses

SG&A expenses for the year ended December 31, 2017 and 2016 were comprised of the following (in thousands):

	Years Ended December 31,		Increase (decrease)	
	2017	2016	$	%
Compensation and benefit related expenses	$23,218	$15,550	$7,668	49.3 %
Stock-based compensation	11,582	11,841	(259)	(2.2)%
Professional fees and other external expenses	30,700	17,763	12,937	72.8 %
Facility related and other internal expenses	13,671	5,525	8,146	147.4 %
Total SG&A expenses	$79,171	$50,679	$28,492	56.2 %

SG&A expenses increased to $79.2 million during the year ended December 31, 2017 from $50.7 million in the same period in 2016. The $28.5 million increase was due to an increase of $12.9 million in consulting fees relating to pre-commercial planning activities, primarily resulting from a one-time payment in October 2017 related to the buy-down of future royalties payable to PARI on the global net sales of ARIKAYCE, an increase of $7.7 million due to higher compensation costs related to an increase in headcount, and an increase of $8.1 million due to higher facility related expenses.

Interest Expense

Interest expense was $5.9 million during the year ended December 31, 2017 as compared to $3.5 million in the same period in 2016. The $2.4 million increase in interest expense in 2017 relates primarily to an increase in our borrowings from Hercules Capital (Hercules) in September and October of 2016. We entered into an Amended and Restated Loan Agreement (A&R Loan Agreement) with Hercules which increased our borrowing capacity by an additional

$30.0 million to an aggregate total of $55.0 million. The increase in borrowings under the A&R Loan Agreement was used to fund the upfront payment owed under the AZ License Agreement for the exclusive global rights to INS1007.

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Income tax (benefit) provision

The income tax (benefit) provision was $(0.3) million and $0.1 million for the years ended December 31, 2017 and 2016, respectively. The income tax (benefit) for the year ended December 31, 2017 reflects the reversal of the valuation allowance related to AMT that we paid in 2009. As a result of the Tax Act, we recorded a noncurrent receivable to reflect the tax amount due to us in future periods relating to a refund due for the prior AMT paid. In addition, the income tax (benefit) provision for the years ended December 31, 2017 and 2016 reflects current income tax expense recorded as a result of taxable income in certain of our subsidiaries in Europe.

LIQUIDITY AND CAPITAL RESOURCES

Overview

There is considerable time and cost associated with developing potential pharmaceutical products to the point of regulatory approval and commercialization. We commenced commercial shipments of ARIKAYCE in October 2018, and to date, have not generated significant revenue from sales of ARIKAYCE. In recent years, we have funded our operations through public offerings of equity securities and debt financings.

In January 2018, we completed an underwritten public offering of $450.0 million aggregate principal amount of Convertible Notes, including the exercise in full of the underwriter's option to purchase additional Convertible Notes. Our net proceeds from the offering, after deducting underwriting discounts and commissions and other offering expenses of $14.2 million, were $435.8 million.

In September 2017, we completed an underwritten public offering of 14,123,150 shares of our common stock, which included the underwriter’s exercise in full of its over-allotment option of 1,842,150 shares, at a price to the public of $28.50 per share. Our net proceeds from the sale of the shares, after deducting underwriting discounts and offering expenses of $24.8 million, were $377.7 million.

We expect to continue to incur operating losses both in our US and certain international entities, as we plan to fund research and development activities and commercial launch activities for ARIKAYCE. We may need to raise additional capital to fund our operations, including the continued commercialization of ARIKAYCE, future clinical trials related to ARIKAYCE, development of INS1007 and INS1009, and the potential development, acquisition, in-license or co-promotion of other products or product candidates that address orphan or rare diseases. We believe we currently have sufficient funds to meet our financial needs for at least the next 12 months. We may opportunistically raise additional capital through equity or debt financing(s), strategic transactions or otherwise. We expect such additional funding, if any, would be used to continue to commercialize ARIKAYCE, to conduct further trials of ARIKAYCE, to develop our product candidates, or to pursue the license or purchase of other technologies or products or product candidates. In 2019, we plan to continue to support the commercial launch of ARIKAYCE in the US, to fund further clinical development of ARIKAYCE and INS1007, and support efforts to obtain regulatory approvals for ARIKAYCE outside the US. Our cash requirements in 2019 will be impacted by a number of factors, the most significant of which are expenses related to the commercialization efforts for ARIKAYCE, and to a lesser extent, expenses related to INS1007 and future ARIKAYCE clinical trials.

Cash Flows

As of December 31, 2018, we had cash and cash equivalents of $495.1 million, as compared with $381.2 million as of December 31, 2017. The $113.9 million increase was due primarily to the net cash proceeds from our issuance of Convertible Notes in January 2018, partially offset by cash used in operating activities and, to a lesser extent, cash used in investing activities. Our working capital was $439.2 million as of December 31, 2018 as compared with $344.8 million as of December 31, 2017.

Net cash used in operating activities was $258.0 million and $159.6 million for the years ended December 31, 2018 and 2017, respectively. The net cash used in operating activities during the years ended December 31, 2018 and 2017 was primarily for the pre-commercialization efforts and clinical activities related to ARIKAYCE, as well as general and administrative expenses. In addition, net cash used in operating activities during the year ended December 31,

2018 and 2017 included commercialization efforts and clinical trial expenses related to INS1007.

Net cash used in investing activities was $14.8 million and $3.0 million for the years ended December 31, 2018 and 2017, respectively. The net cash used in investing activities during 2018 was primarily related to the investment in our long-term production capacity build-out at Patheon. The net cash used in investing activities during 2017 was primarily related to the investment in our long-term production capacity build-out at Patheon and for the build out of our lab facility in Bridgewater,

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New Jersey. We expect our net cash used in investing activities will increase in 2019 as compared to 2018 as a result of our continuing investment in the build-out of Patheon and our new headquarters facility.

Net cash provided by financing activities was $386.7 million and $381.1 million for the years ended December 31, 2018 and 2017, respectively. Net cash pr