Making big health problems a smaller part of life

insmed®

"As we evolve, our commitment to patients with rare and serious diseases remains unchanged."

We are pleased to report on a truly phenomenal year for Insmed® as we advanced our mission to transform the lives of patients with serious and rare diseases. In 2019, we made tremendous progress in serving patients in the U.S. with refractory *Mycobacterium avium* complex (MAC) lung disease; enhanced our global operations to prepare to serve appropriate patients in Europe and Japan, if our marketing applications are approved; and advanced a research and development pipeline with significant potential to address the unmet needs patients with rare diseases continue to face.

We also moved into a state-of-the-art global headquarters in New Jersey and grew to more than 425 employees around the world. We are incredibly proud of our people—they represent the best talent in the industry and always operate with a patients-first mentality.

2019 was the first full year of commercialization for ARIKAYCE® (amikacin liposome inhalation suspension)—Insmed's first approved therapy and the first and only medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of MAC lung disease as part of a combination antibacterial drug regimen for adult patients who have limited or no alternative treatment options.

MAC lung disease is a chronic, debilitating condition that can cause severe and permanent lung damage. For patients with refractory disease, the availability of an approved therapy is incredibly meaningful. We are very pleased with the progress we made in bringing ARIKAYCE to appropriate U.S. patients. Importantly, as of the end of 2019, more than 1,900 U.S. physicians had prescribed ARIKAYCE.

The success of the ARIKAYCE launch in the U.S. is only the beginning. We are working to initiate a post-approval confirmatory study of ARIKAYCE in a front-line setting of patients with MAC lung disease in the second half of 2020. We have also filed for approval of ARIKAYCE in both Europe and Japan and, if approved, would expect to launch in Germany by the end of 2020. We are eager to serve patients in these areas with the same level of dedication as we have in the U.S.

We were thrilled to report in early 2020 that, based on top-line data, our global, Phase 2 study of INS1007 in patients with non-cystic fibrosis bronchiectasis achieved both its primary and key secondary endpoints. INS1007 is a novel, oral, reversible DPP1 inhibitor that we believe represents a promising new approach to modulating neutrophil activity. As we advance INS1007 to Phase 3 development for bronchiectasis, we are excited by its potential in a range of diseases.

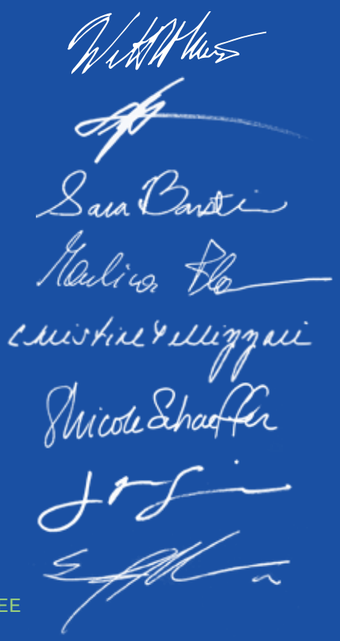
We are also advancing INS1009, a dry powder, inhaled treprostinil prodrug formulation, into Phase 1 development for pulmonary arterial hypertension.

2019 was the strongest year in Insmed's history, and we begin 2020 with a wealth of opportunity ahead. Importantly, we have strengthened our leadership team with several recent appointments and have taken a disciplined approach to resourcing as we fund the activities that will drive our growth.

As we evolve, our commitment to patients with rare and serious diseases remains unchanged. We are proud to take on some of the biggest health challenges to make them a smaller part of patients' lives.

Thank you to our shareholders, Board of Directors, employees, and most of all the healthcare professionals, patients, and families we serve.

THE INSMED EXECUTIVE COMMITTEE



We're taking on big health challenges to make them a smaller part of patients' lives.

A MISSION TO TRANSFORM At Insmed, we are on a mission to transform the lives of patients living with serious and rare diseases. We champion those who are overlooked and underserved and are dedicated to supporting patients along their journey.

THE VISION TO MAKE IT HAPPEN Our vision is to be a globally recognized leading biotech company that empowers great people to deliver, with a profound sense of urgency and compassion, life-altering therapies to small patient populations experiencing big health problems.

"Our role is to have a positive impact on the lives of patients with poorly understood diseases. It drives every decision we make."

Insmed's dedication to patients is not just a company tagline. It is an active promise to join their fight—to take a stand to pursue unmet needs and to work quickly and creatively to deliver meaningful results. In everything we do, we put patients first—we talk with patients, listen to patients, and conduct our research with input from patients.

RECEIVED

TWO

KEY PATENTS FOR ARIKAYCE
—one in the U.S. and one in Europe—extending patent exclusivity into 2035 in these markets

MARKED THE

First Full Year

OF LAUNCH FOR ARIKAYCE IN THE U.S.

SUBMITTED APPLICATIONS FOR THE APPROVAL OF ARIKAYCE IN EUROPE AND JAPAN

ADVANCED ARIKAYCE LIFE-CYCLE MANAGEMENT PROGRAMS AND A PROMISING EARLIER-STAGE PIPELINE

Opened a new, state-of-the-art global headquarters in Bridgewater, NJ

REPORTED POSITIVE TOP-LINE RESULTS FROM PHASE 2 WILLOW STUDY OF INS1007 IN NON-CYSTIC FIBROSIS BRONCHIECTASIS

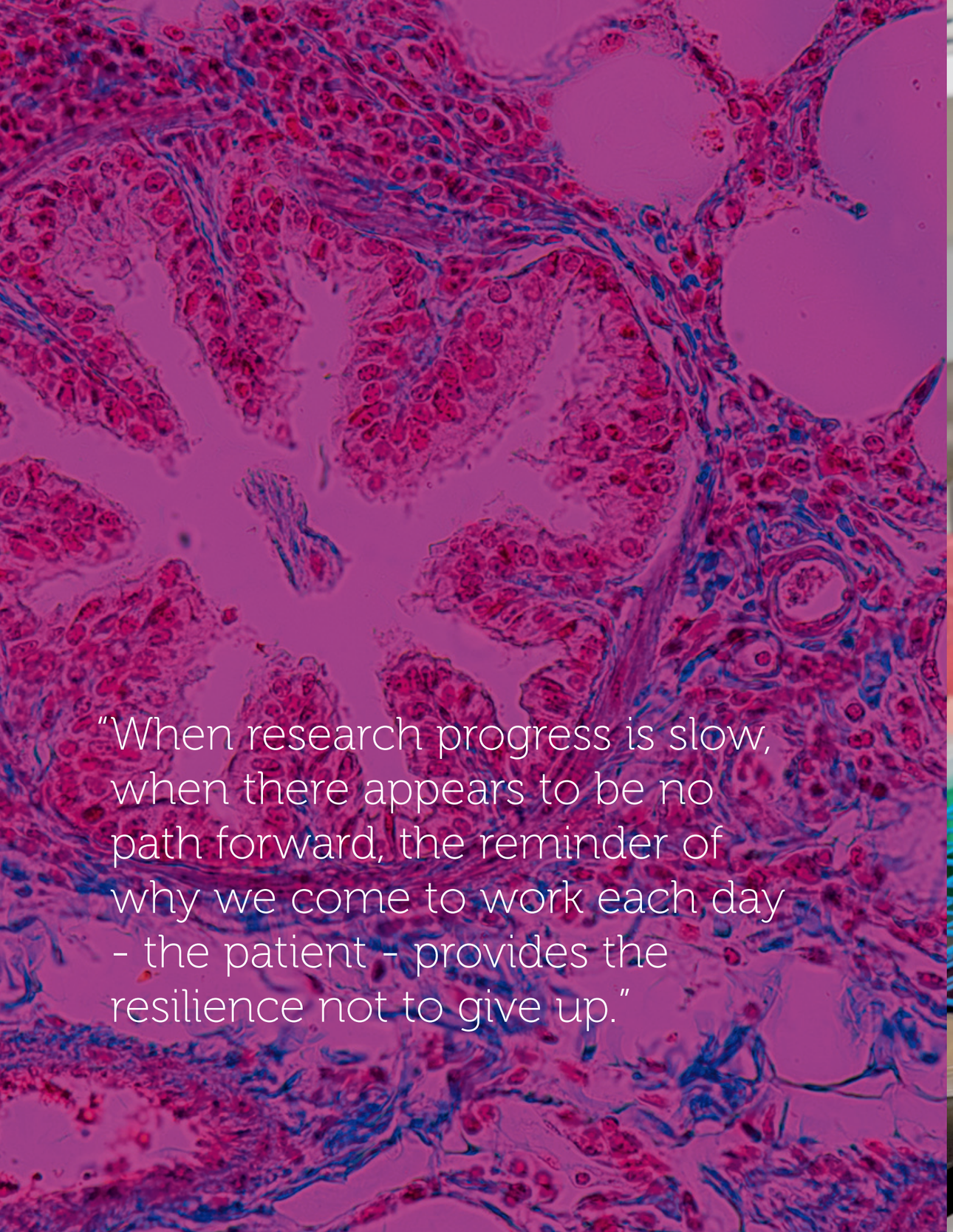
EXPANDED GLOBALLY WITH THE OPENING OF OUR TOKYO OFFICE

Grew to more than 425 colleagues worldwide

"I care because I have a voice that a patient may not have, because I can educate a clinician, and because I can make a difference in someone's life."

"When I was diagnosed with NTM lung disease, it sounded very scary. I was alone, I was frightened. Having a support network means a great deal to me."

Beth was living her dream, with a successful career and an active lifestyle. But she soon developed a debilitating cough that interrupted both her personal and professional life. Her symptoms, which also included fatigue and weight loss, progressed with no clear answer. After two years, Beth was finally diagnosed with nontuberculous mycobacterial (NTM) lung disease. While the news was frightening, she was relieved to have an accurate diagnosis and a path forward. For Beth, educating herself about the disease, working with a respiratory specialist, and finding a network of other patients have helped her manage life with NTM lung disease.



"When research progress is slow, when there appears to be no path forward, the reminder of why we come to work each day - the patient - provides the resilience not to give up."

OUR VALUES

Collaboration

We check our egos at the door and share ideas openly and candidly. When we disagree, we do so with respect and a willingness to listen.

Accountability

We are each responsible for ensuring that our actions align with our values.

Passion

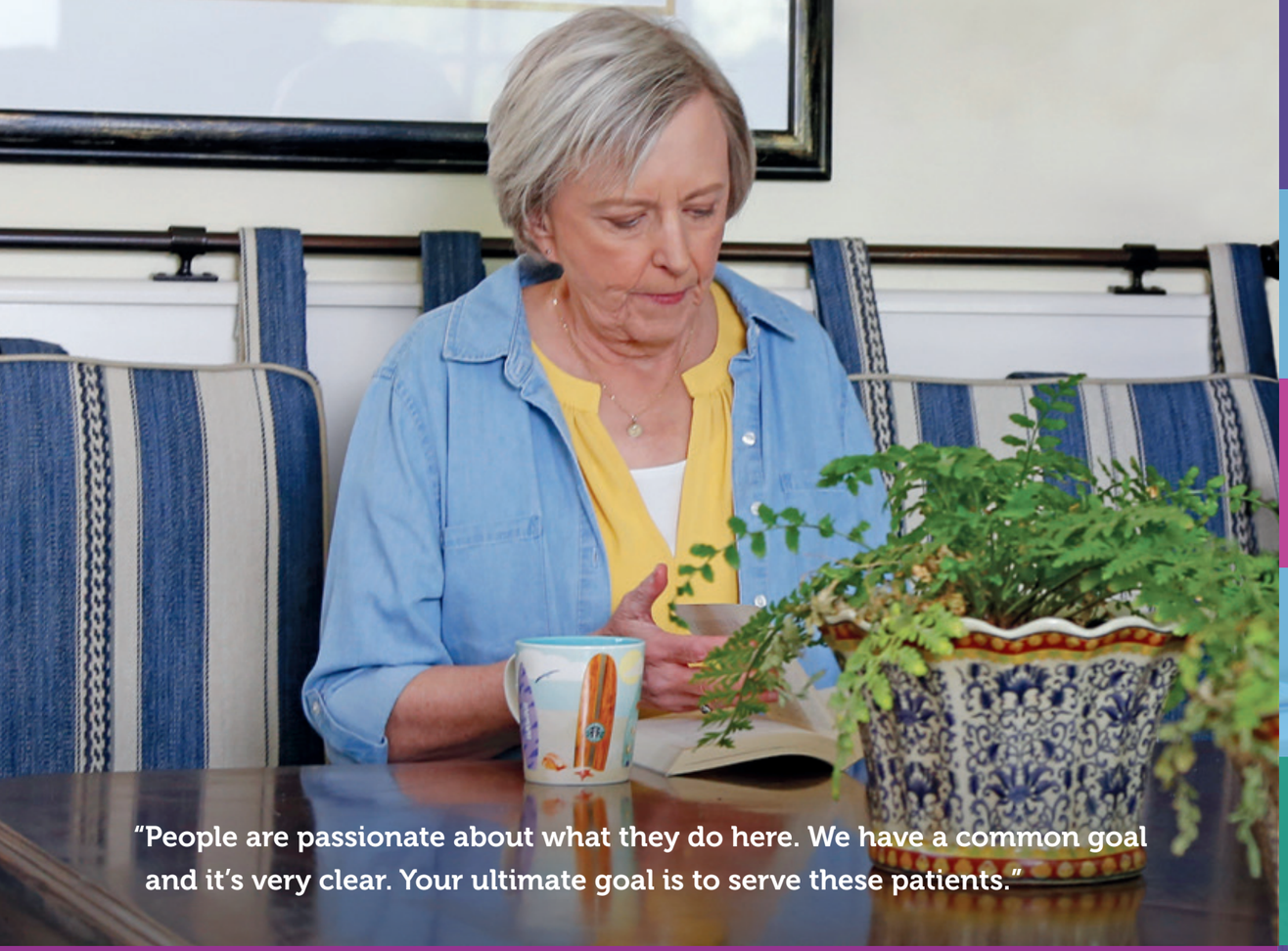
We are driven to expect more than others think is possible and deliver excellence to our patients, colleagues, and stakeholders.

Respect

We embrace our colleagues' differences, recognize their contributions, and create a culture of empowerment and trust.

Integrity

We are committed to acting in an ethical, honest, and transparent manner in everything we do.



"People are passionate about what they do here. We have a common goal and it's very clear. Your ultimate goal is to serve these patients."

250
holiday cards sent to men and women in the military

100
holiday gift wishes granted to Somerset County, NJ, residents

75
pounds of candy donated to veterans

50
Thanksgiving place settings created for homeless individuals

100
comfort kits assembled for disaster victims

At Insmed, we are powered by purpose. A purpose to serve patients and their families with unwavering dedication. A purpose to find solutions where there were none before. A purpose to do what's right, even when it isn't easy. Our patient-centered culture is rooted in this shared sense of purpose. We don't always have a defined play book, but we operate with passion and creativity to come up with the best path forward.

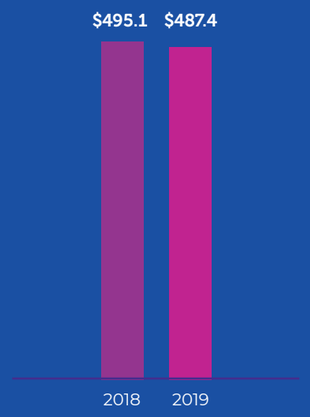
In 2019, our employee base grew significantly to support the growing needs of our business. While our talents and backgrounds are varied, we all share the same sense of responsibility to small patient populations experiencing big health problems. We are proud of the culture we have built and continue to maintain even as we grow.

Importantly, a big part of our culture is engaging with our colleagues and giving back to the communities in which we live and work. Whether we're assembling disaster relief kits or running a 5K, these activities help us get to know our fellow employees and exercise creativity and passion outside the office.

"It's open, it's informal, and people are trusted to make the right decisions."

2019
NET PRODUCT SALES
BY QUARTER
(IN MILLIONS)

CASH AND
CASH EQUIVALENTS
(IN MILLIONS)



"It's a culture of empowerment, which organically motivates us to do a good job and come to the table with a creative mindset."

"I am proud of our team's performance in the first full year of the ARIKAYCE U.S. launch, and we look forward to serving even more patients as we prepare for potential approvals in Europe and Japan. With positive top-line Phase 2 data for INS1007 in non-cystic fibrosis bronchiectasis and other meaningful advancements in our pipeline, we are well on our way toward building a robust portfolio that addresses the unmet needs of small patient populations experiencing big health problems."

– WILL LEWIS, CHAIRMAN & CEO

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2019

OR

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

For the transition period from _____ to _____

Commission File Number 0-30739

INSMED INCORPORATED

(Exact name of registrant as specified in its charter)

Virginia	**54-1972729**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. employer identification no.)**
700 US Highway 202/206 Bridgewater, New Jersey 08807 (Address of principal executive offices)	**(908) 977-9900 (Registrant's telephone number including area code)**

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

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

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

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

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 ☒

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 ☒ 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 ☒ No ☐

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 ☒ 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 ☒

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant on June 30, 2019, was $2.3 billion (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 21, 2020, there were 89,775,696 shares of the registrant's common stock, $0.01 par value, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for its 2020 Annual Meeting of Shareholders to be filed with the Securities and Exchange Commission no later than April 29, 2020 and to be delivered to shareholders in connection with the 2020 Annual Meeting of Shareholders, are herein incorporated by reference in Part III of this Annual Report on Form 10-K.

INSMED INCORPORATED

INDEX

Unless the context otherwise indicates, references in this Annual Report on Form 10-K to “Insmed Incorporated” refers to Insmed Incorporated, a Virginia corporation, and the “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 Annual Report on Form 10-K also contains trademarks of third parties. Each trademark of another company appearing in this Annual Report on Form 10-K is the property of its owner.

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 United States (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 healthcare community;*
- *our inability to obtain full approval of ARIKAYCE from the US Food and Drug Administration (FDA), including the risk that we will not timely and successfully complete the study to validate a patient reported outcome (PRO) tool and 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, expected rates of patient uptake, duration of expected treatment, or expected patient adherence or discontinuation rates;*
- *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;*
- *risks that the full set of data from the WILLOW study, our six-month Phase 2 trial of INS1007 in patients with non-CF bronchiectasis (NCFBE) will not be consistent with the top-line results of the study;*
- *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, or delays in obtaining, regulatory approvals for ARIKAYCE outside the US or for our product candidates in the US, Europe, Japan or other markets, including the United Kingdom as a result of the United Kingdom's recent exit from the European Union;*
- *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 or agreements with us;*

- *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;*
- *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, including any pricing reform, and failure to comply with such laws and regulations;*
- *inability to repay our existing indebtedness and uncertainties with respect to our ability to access future capital; and*
- *delays in the execution of plans to build out an additional FDA-approved third-party manufacturing facility and unexpected expenses associated with those plans.*

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 Form 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.

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, received accelerated approval in the US in September 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 six consecutive months of a multidrug background regimen therapy. Nontuberculous mycobacterial (NTM) lung disease caused by MAC (which we refer to as 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 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 the execution of the successful commercialization of ARIKAYCE in the US. The product was granted accelerated approval by the FDA 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. We began commercial shipments of ARIKAYCE in October 2018. • In July 2019, we filed a marketing authorization application (MAA) with the European Medicines Agency (EMA) for ARIKAYCE for the treatment of patients with persistent MAC lung infection. The MAA filing was subsequently validated. • 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.	• In addition to our MAA, we intend to submit regulatory filings for ARIKAYCE in Japan in the first quarter of 2020. If approved by the relevant regulatory authorities, we expect ARIKAYCE would be the first inhaled therapy specifically indicated for the treatment of MAC lung disease in Europe and Japan. • If approved by the relevant regulatory authorities, we plan to commercialize ARIKAYCE in certain countries in Europe, Japan and certain other countries. • We continue to collaborate with the FDA on the post-approval confirmatory clinical trial required for full approval. We have initiated efforts to evaluate an appropriate patient reported outcome (PRO) tool through a short-term study, to enable the assessment of therapies for the treatment of NTM lung disease. In parallel, we plan to begin the confirmatory clinical study of ARIKAYCE in a front-line setting of patients with MAC lung disease in the second half of 2020. In addition, we intend to conduct a separate study in patients with NTM lung disease caused by M. abscessus.
INS1007 (oral reversible inhibitor of DPP1) for NCFBE and other rare diseases	• In February 2020, we announced top-line results from our global, randomized, double-blind placebo-controlled Phase 2 WILLOW study evaluating the efficacy, safety, and pharmacokinetics of INS1007 administered once daily in adults with NCFBE. • Top-line results for the WILLOW study reflect that the study met its primary endpoint of time to first pulmonary exacerbation over the 24-week treatment period for both the 10 mg and 25 mg dosage groups of INS1007 compared to placebo (p=0.027, p=0.044, respectively). In addition, treatment with INS1007 resulted in a reduction in the frequency of pulmonary exacerbations, a key secondary endpoint, versus placebo.	• We plan to design and conduct a Phase 3 program through which we will seek to confirm the positive results seen in the WILLOW study. This study will primarily investigate INS1007 in NCFBE and we expect the primary endpoint will be frequency of pulmonary exacerbations. • We are also 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 a Phase 1 study of nebulized 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. We are advancing INS1009 as an inhaled dry powder formulation to a Phase 1 study.

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

Our strategy focuses on the needs of patients with rare diseases. We secured accelerated approval from the FDA of ARIKAYCE for the treatment of refractory MAC lung disease in patients with limited or no alternative treatment options, and currently are primarily focused on the successful commercialization of ARIKAYCE. We are also seeking regulatory approval in Europe and Japan. 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 the successful commercialization of ARIKAYCE;
- Develop and validate a PRO tool for NTM lung disease to be used in, among other trials, the confirmatory clinical trial required for the full US approval of ARIKAYCE by the FDA in patients with MAC lung disease;
- Continue our global expansion efforts in Europe and Japan to support pre-commercial activities in those regions and support the potential regulatory filings for ARIKAYCE in Japan in the first quarter of 2020;
- Advance our pipeline, which is intended to bring additional therapies to market for patients with serious and rare diseases, including designing and conducting a Phase 3 program of INS1007 in patients with bronchiectasis;
- Ensure our product supply chain will support the global commercialization and potential future lifecycle management programs of ARIKAYCE;
- Develop a core value dossier to support payor reimbursement for ARIKAYCE in the US, Europe and Japan;
- Maintain or 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, including 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;
- Advance INS1009 for use as an inhaled dry powder formulation in PAH to a Phase 1 study and generate preclinical findings from our earlier-stage programs; and
- Expand our pipeline through corporate development.

ARIKAYCE for Patients with MAC Lung Disease

ARIKAYCE is our first approved product. ARIKAYCE received accelerated approval in the US in September 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. 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.

Accelerated Approval

In March 2018, we submitted a new drug application (NDA) for ARIKAYCE to the FDA to request accelerated approval. 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. In September 2018, the FDA granted accelerated 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 the FDA, will be designed 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. We have initiated efforts to evaluate an appropriate PRO tool through a short-term study to enable the assessment of therapies for the treatment of NTM lung disease. In parallel, we plan to begin a confirmatory clinical study of ARIKAYCE in a front-line setting of patients with MAC lung disease in the second half of 2020. In addition, we intend to conduct a separate study in patients with NTM lung disease caused by *M. abscessus*. We continue to collaborate with the FDA on the timetable as well as the design and validation of the PRO and the post-approval confirmatory clinical trial. The full approval of ARIKAYCE will be contingent upon verification and description of clinical benefit in the post-approval confirmatory study.

Regulatory Pathway Outside of the US

Our regulatory filing in Europe was submitted in July 2019 and subsequently validated by the EMA. The EMA will primarily focus on the proportion of patients who maintained durable culture conversion for three months off all therapy on ARIKAYCE plus GBT compared to GBT only. We intend to submit regulatory filings for ARIKAYCE in Japan in the first quarter of 2020.

Clinical Trials

Accelerated approval of ARIKAYCE was supported by preliminary data from the 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. In May 2019, we presented at the American Thoracic Society meeting that 41/65 (63.1%) of patients on ARIKAYCE plus GBT who had achieved culture conversion by Month 6 had maintained durable culture conversion for three months off all therapy compared to 0/10 (0%) on GBT only ($p<0.0002$). Safety data for these patients were consistent with safety data previously reported for patients by Month 6 of the CONVERT study.

Patients who did not culture convert by Month 6 may have been eligible to enroll in the 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 and final efficacy data regarding culture conversion were consistent with these interim data. We have analyzed the safety and efficacy data from the 312 study, and we did not observe any new safety signals.

Further Research and Lifecycle Management

We are currently exploring and supporting research and lifecycle management programs for ARIKAYCE 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 study designs focusing on the MAC lung disease 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 have initiated efforts to evaluate an appropriate PRO tool through a short-term study, to enable the assessment of therapies for the treatment of NTM lung disease. In parallel, we plan to begin the confirmatory clinical study of ARIKAYCE in a front-line setting of patients with MAC lung disease in the second half of 2020.

Subsequent lifecycle management studies could also potentially enable us to reach more patients. The use of ARIKAYCE to treat infections caused by non-MAC NTM species is being evaluated. For instance, we plan to conduct a study in patients with NTM lung disease caused by *M. abscessus*. These initiatives also 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. Using information from external sources, including market research funded by us and third parties, and internal analyses and calculations, we currently estimate potential patient populations 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	95,000-115,000	48,000-55,000	12,000-17,000
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 (ATS/IDSA), 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 Europe and Japan. We submitted our regulatory filing in Europe in July 2019. 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). We intend to submit regulatory filings in Japan in the first quarter of 2020. We have 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. We are developing INS1007 for the treatment of patients with bronchiectasis. DPP1 is an enzyme responsible for activating NSPs 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 NSPs (including neutrophil elastase (NE), 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 result in excessive active NSPs that cause lung destruction and inflammation. INS1007 may decrease the damaging effects of inflammatory diseases such as NCFBE by inhibiting DPP1 and its activation of NSPs.

NCFBE is a severe, chronic pulmonary disorder in which the bronchi become permanently dilated due to a cycle of infection, inflammation, and lung tissue damage. The condition is marked by frequent pulmonary exacerbations requiring antibiotic therapy and/or hospitalizations. Symptoms include chronic cough, excessive sputum production, shortness of breath, and repeated respiratory infections, which can worsen the underlying condition. NCFBE affects approximately 340,000 to

520,000 patients in the US. Currently, there is no cure, and there are no approved therapies specifically targeting NCFBE in the US, Europe, or Japan. We are also exploring the potential of INS1007 in various neutrophil-driven inflammatory conditions.

As a result of the positive results of the WILLOW study discussed below, we plan to design and conduct a Phase 3 program, which will primarily investigate INS1007 in NCFBE. Based on indications from the FDA, we expect that the primary endpoint in the study will be frequency of pulmonary exacerbation.

The WILLOW Study

The WILLOW study was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, multi-national, Phase 2 study to assess the efficacy, safety and tolerability, and pharmacokinetics of INS1007 administered once daily for 24 weeks in patients with NCFBE. The WILLOW study was conducted at 116 sites and enrolled 256 adult patients diagnosed with NCFBE who had at least two documented pulmonary exacerbations in the 12 months prior to screening. Patients were randomized 1:1:1 to receive either 10 mg or 25 mg of INS1007 or matching placebo. The primary efficacy endpoint was the time to first pulmonary exacerbation over the 24-week treatment period in the INS1007 arms compared to the placebo arm.

WILLOW Top-Line Efficacy Data

We announced top-line data for the WILLOW study in February 2020. The top-line data demonstrates that the WILLOW study met its primary endpoint of time to first pulmonary exacerbation over the 24-week treatment period for both the 10 mg and 25 mg dosage groups of INS1007 compared to placebo (p=0.027, p=0.044, respectively). In addition, treatment with INS1007 resulted in a reduction in the frequency of pulmonary exacerbations, a key secondary endpoint, versus placebo. Specifically, patients treated with INS1007 experienced a 36% reduction in the 10 mg arm (p=0.041) and a 25% reduction in the 25 mg arm (p=0.167) versus placebo. Change in concentration of active NE in sputum versus placebo from baseline to the end of the treatment period was also statistically significant (p=0.034 for 10 mg, p=0.021 for 25 mg).

WILLOW Top-Line Safety and Tolerability Data

INS1007 was generally well-tolerated in the study. Rates of adverse events (AEs) leading to discontinuation in patients treated with placebo, INS1007 10 mg, and INS1007 25 mg were 10.6%, 7.4%, and 6.7%, respectively. The most common AEs in patients treated with INS1007 were cough, headache, sputum increase, dyspnea, fatigue, and upper respiratory tract infection. Rates of adverse events of special interest (AESIs) in patients treated with placebo, INS1007 10 mg, and INS1007 25 mg, respectively, were as follows: rates of periodontal disease were 2.4%, 7.4%, and 10.1%; rates of hyperkeratosis were 0%, 3.7%, and 1.1%; and rates of infections that were considered AESIs were 18.8%, 16.0%, and 16.9%.

Further Research

In August 2019, we received notice from the FDA that we were awarded a development grant of $1.8 million for specific work to be performed on a PRO tool over the next two years. The grant funding is for the development of a novel PRO tool for use in clinical trials to measure symptoms in patients with NCFBE with and without NTM lung infection.

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 advancing its development to a Phase 1 study as an inhaled dry powder formulation.

Corporate Development

We plan to continue to develop, acquire, in license or co-promote other products and product candidates, including those 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 aggregate investment to increase the long-term production capacity, including under 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 (the Commercialization Agreement).

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 425 issued patents and pending patent applications in the US and in foreign countries, including more than 250 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.

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 10 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)
- US Patent No. 10,251,900 (expires May 15, 2035)

In addition, we own five pending US patent applications that cover the ARIKAYCE composition and/or its use in treating NTM, including MAC lung infections. We also own a pending US application that covers methods for making ARIKAYCE. One or more of these patent applications, if issued as patents in their current form, may be eligible for listing in the FDA Orange Book for ARIKAYCE. We anticipate that in the US, we will have potential patent coverage for ARIKAYCE and its use in treating NTM lung disease, including NTM lung disease caused by MAC, through May 15, 2035.

Six patents have been granted by the European Patent Office (EPO) (European Patent Nos. 1581236, 1909759, 1962805, 2363114, 2823820 and 3142643) that relate to ARIKAYCE and its use in treating NTM, including MAC lung infections. 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. 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. The appeal hearing is scheduled to take place on March 31, 2020 in Munich, Germany. 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. European Patent No. 3142643 expires May 15, 2035 and includes claims related to ARIKAYCE and its use for treating MAC lung infections.

More than 60 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 30 foreign patent applications are pending that relate to the ARIKAYCE composition and/or its use in treating various pulmonary disorders, including NTM lung disease.

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.

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, 9,815,805 and 10,287,258, which have claims related to INS1007 and methods for using INS1007. Each of these patents 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 two registrations for the INSMED mark and one registration for the ARIKAYCE mark from the US Patent and Trademark Office (USPTO). We have also received notices of allowance or registrations in a number of countries abroad for the INSMED and ARIKAYCE marks, among others. The 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

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 the system with ARIKAYCE for the treatment of such indications, but we cannot manufacture the nebulizers except as permitted under our Commercialization Agreement with PARI, which is described in further detail below. Lamira has been approved for use in the US (in combination with ARIKAYCE) and EU. We also currently have rights to use the nebulizers in expanded access programs and clinical trials. Lamira 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 outside the US and EU.

We have certain obligations under this licensing agreement in relation to specified licensed indications. 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. 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. 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 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 made additional milestone payments of €1.0 million and €1.5 million, respectively, to PARI. In addition, PARI is entitled to receive a future milestone payment of €0.5 million in cash based on receipt of the first 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.

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 a minimum of $6 million for commercial ARIKAYCE batches produced and certain manufacturing activities 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.

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.

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 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 aggregate investment to increase our long-term production capacity, 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. In April 2015, we entered into a work order with Synteract to perform implementation and management services for the 312 study. As of December 31, 2019, substantially all costs related to the CONVERT and 312 studies had been incurred.

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 in research funding for the development of ARIKAYCE. As a result of the US approval of ARIKAYCE and in accordance with the agreements, as amended, we owe milestone payments to CFFT of $13.4 million in the aggregate, which are payable through 2025. In addition, if certain global sales milestones are met within five years of ARIKAYCE's commercialization, we would owe additional payments of up to $3.9 million. We have estimated the likelihood of meeting the global sales milestones and have accrued for these contingent obligations proportionally based on net sales of ARIKAYCE.

INS1007-related Agreements

Syneos Health (Syneos)

We entered into a services agreement with 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 $23 million over the period of the study.

AstraZeneca

In October 2016, we entered into a license agreement with AstraZeneca (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. The next contingent milestone payment to AstraZeneca is $12.5 million and is due upon first dosing in a Phase 3 study. 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 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.

In the 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 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 orphan designation as well. The period of orphan exclusivity is 10 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, EU 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 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 new molecular entity (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 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 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 anti-fungal 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.

Medical Device Regulation

Medical devices, such as Lamira, 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 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 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.

Medical devices are generally governed by Directive 93/42/EEC on Medical Devices (Directive 93/42) 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. Lamira 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 reassess 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 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 (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. Furthermore, we must obtain any required pricing approvals in addition to regulatory approval prior to launching a product candidate in the approving country. The discussion of EU government regulations also applies to the United Kingdom.

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 healthcare 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 healthcare 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.

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 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 healthcare 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 product 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 healthcare 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 healthcare products. In the US and most other jurisdictions, numerous detailed requirements apply to government and private healthcare 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, 2019, we had a total of 435 employees: 168 in research, clinical, regulatory, medical affairs and quality assurance; 36 in technical operations, manufacturing and quality control; 85 in general and administrative functions; and 146 in commercial activities. We had 373 employees in the US, 47 employees in Europe and 15 employees in Japan. We anticipate increasing our headcount in 2020.

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 "Investors-Corporate Governance" page are charters for the Audit, Compensation, Nominations and Governance and Science and Technology Committees of our board of directors, our Corporate Governance Guidelines, 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.

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 nontuberculous mycobacterial (NTM) lung disease caused by MAC (which we refer to as 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 commercialization 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 was 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 healthcare community.

Despite receiving US Food and Drug Administration (FDA) approval of ARIKAYCE market acceptance may vary among physicians, patients, third-party payors or others in the healthcare 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 not likely that we will continue to 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 healthcare community on the benefits of ARIKAYCE has required and will continue to require significant resources, which may be greater than those required to commercialize more established technologies and these efforts 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

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.

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 patients with MAC lung disease. Pursuant to the timetable agreed upon with the FDA when the approval letter of ARIKAYCE was received, confirmatory trial results are to be reported by 2024. We have initiated efforts to evaluate an appropriate patient reported outcome (PRO) tool through a short-term study to enable the assessment of ARIKAYCE for the treatment of MAC lung disease. In parallel, we plan to begin a confirmatory clinical study of ARIKAYCE in a front-line setting of patients with MAC lung disease in the second half of 2020. We continue to collaborate with the FDA on this timetable as well as the design and validation of the PRO and the post-approval confirmatory clinical trial. 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, the design of the trial itself and the PRO, and if our PRO is not validated, we would need to develop a new clinical endpoint for the trial. We may also 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, 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 information and payments to healthcare professionals and healthcare 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
- 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 healthcare 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.

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 governmental 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. Since commercializing ARIKAYCE, payors have evaluated ARIKAYCE for inclusion on formularies. Going forward, we may not be able to provide data sufficient to gain positive coverage and reimbursement determinations 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. Payors have restricted and may also continue to restrict coverage of 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. 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 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. For instance, we have observed an increase in the time to fill prescriptions, particularly for patients that are insured through Medicare, in the first quarter of the year as a result of the donut hole, and, while we do not expect this situation to extend through the entire year, this situation may recur in the first quarter of subsequent years. We expect further federal and state proposals and healthcare 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 Annual Report on Form 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.

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 government agencies in EU countries 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 healthcare 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 is now being 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 external sources, including market research funded by us and third parties, and 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 other jurisdictions in which we are seeking or plan to 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 from such product candidates, 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 global marketing and sales organization, and we have limited experience 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 using our sales force, but we may not continue to be successful in these efforts. If ARIKAYCE receives marketing approval in Europe, we plan to expand our sales force to support those commercialization efforts. The establishment, development and maintenance 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

The reported results of the WILLOW study are based on top-line data and may differ from complete study results once additional data are evaluated.

The reported results of our WILLOW study, which are discussed herein, consist of only top-line data from the study. Top-line data are based on a preliminary analysis of currently available efficacy and safety data, and therefore these reported results are subject to change following a comprehensive review of the more extensive data we expect to receive for patients in the study. Top-line data are based on important assumptions, estimations, calculations and information available to us, and we have not received all analytical outputs to evaluate all of the data from the WILLOW study. As a result, the top-line data results may differ from the complete data, or different conclusions or considerations may qualify such top-line results, once the complete data have been fully evaluated. If these top-line data differ from the results of the full data for the WILLOW study, our ability to continue development of, and ultimately seek regulatory approval for, INS1007 may be harmed, which could materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock.

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:

- 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.

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 sufficient 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 ARIKAYCE is approved outside of the US or if another 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 routinely assess regulatory strategies which could expedite the development and regulatory review of our product candidates in the US and other markets, but we may be unsuccessful in pursuing such strategies. The FDA has denied our request for orphan drug designation for INS1007 in NCFBE. 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, Inc. (Transave), and we have limited experience in conducting and managing the preclinical development activities and clinical trials necessary to obtain regulatory approvals, including approval by the FDA, 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 relevant 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, 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.

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. We currently rely on Therapure Biopharma Inc. (Therapure) and Ajinimoto Althea, Inc. (Althea) to provide our clinical and commercial supply of ARIKAYCE, and intend to rely on Patheon in the future. 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. 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 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 would likely 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 "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 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 commercialization of ARIKAYCE in the US and international expansion efforts, 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 to support our commercialization 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 or other liabilities 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.

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.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, our proprietary business information and that of our suppliers, as well as personally identifiable information of clinical trial participants and employees. 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. Such an event 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. In addition, the loss of clinical trial data for our product candidates could result in delays in our regulatory submission and approval efforts and significantly increase our costs to recover or reproduce the data, if possible. 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, 2019, we had 47 employees located in Europe and 15 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 exit from 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, following the transition period, UK regulatory actions; and
- Compliance with foreign or US laws, rules and regulations, including data privacy requirements, labor relations laws, 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 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 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 lung disease and are seeking to advance studies in lung disease, including NTM lung disease caused by mycobacterial species other than MAC. 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 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 Annual Report on Form 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 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 Annual Report on Form 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 payments 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.

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 healthcare 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 healthcare 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. In December 2019, the US Court of Appeals for the Fifth Circuit found the individual mandate to be unconstitutional and remanded the case to the district court to determine whether the individual mandate provision is severable from the rest of the law. The district court's ruling remains stayed pending appeal. 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 Annual Report on Form 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 healthcare 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 healthcare "fraud and abuse" laws, including anti-kickback laws, false claims laws and other laws intended to reduce fraud and abuse in federal and state healthcare 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 healthcare 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, 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 healthcare 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 requirements, and we could be subject to penalties if it is determined that we have failed to comply with an applicable legal 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 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. We conducted the 312 study and the WILLOW study, our global Phase 2 study of INS1007 in NCFBE, 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 10 years. See *Business-Government Regulation-Orphan Drug Designation* in Item 1 of Part I of this Annual Report on Form 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.

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 & Co, Inc. As of December 31, 2019, our accumulated deficit was $1.5 billion. For the years ended December 31, 2019, 2018 and 2017, our consolidated net loss was $254.3 million, $324.3 million and $192.6 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 commercialization 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 increase of production capacity at Patheon and process improvements in order to manufacture at a larger 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 for ARIKAYCE 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 for other purposes, including to resolve litigation. As of December 31, 2019, we had $487.4 million of cash and cash equivalents on hand. Our operating expenses, capital expenditures and long-term investments were significantly higher in 2019 than in 2018, 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;
- 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; and
- 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, after the quarter ending March 31, 2018, holders may convert their Convertible Notes at their option during any quarter (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 7% of our total assets as of December 31, 2019. 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, 2019, the balance of these intangibles, net of amortization was $52.1 million and $1.5 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 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.

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.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

We currently lease 117,022 square feet of office space for our corporate headquarters in Bridgewater, New Jersey. We have a one-time option to expand the leased premises by up to 50,000 square feet prior to the fifth anniversary of the initial lease commencement, which occurred in the fourth quarter of 2019. The initial term of this lease will expire in 2030.

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

PART II

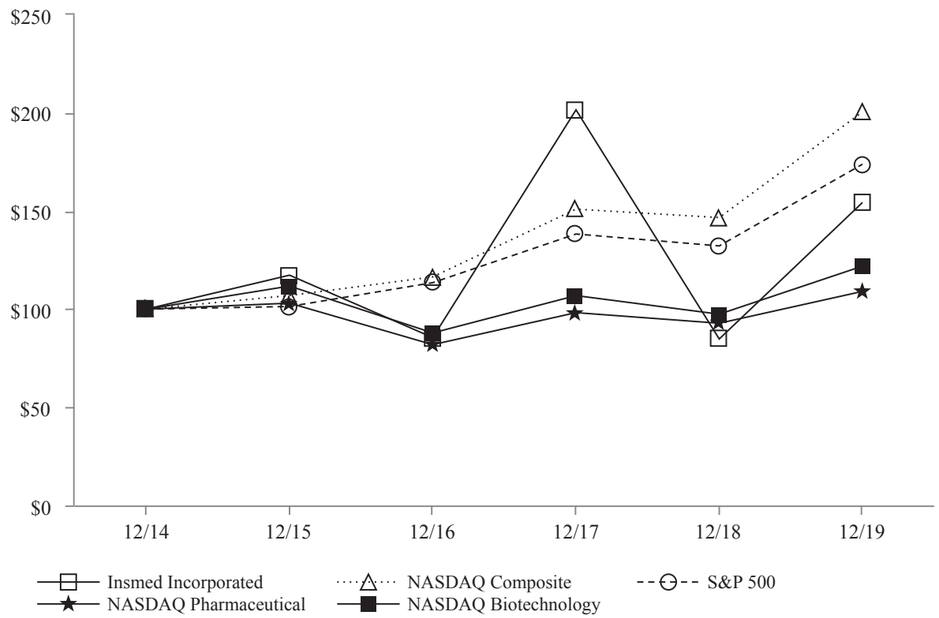
ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

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

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.

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 12/31/14 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, 2019, 2018, 2017, 2016 and 2015. 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.

	Year Ended December 31,				
	2019	2018	2017	2016	2015
	(in thousands, except per share data)				
Statement of Operations Data:					
Revenues	$ 136,467	$ 9,835	$ —	$ —	$ —
Cost of product revenues (excluding amortization of intangible assets)	24,212	2,423	—	—	—
Gross profit	112,255	7,412	—	—	—
Operating expenses:					
Research and development	131,711	145,283	109,749	122,721	74,277
Selling, general and administrative	210,796	168,218	79,171	50,679	43,216
Amortization of intangible assets	4,993	1,249	—	—	—
Total operating expenses	347,500	314,750	188,920	173,400	117,493
Operating loss	(235,245)	(307,338)	(188,920)	(173,400)	(117,493)
Investment income	9,921	10,341	1,624	604	261
Interest expense	(27,705)	(25,472)	(5,925)	(3,498)	(2,889)
Loss on extinguishment of debt	—	(2,209)	—	—	—
Other income (expense), net	(531)	602	300	119	(33)
Loss before income taxes	(253,560)	(324,076)	(192,921)	(176,175)	(120,154)
Income tax provision (benefit)	777	201	(272)	98	(1,971)
Net loss	$ (254,337)	$ (324,277)	$ (192,649)	$ (176,273)	$ (118,183)
Basic and diluted net loss per share	$ (3.01)	$ (4.22)	$ (2.89)	$ (2.85)	$ (2.02)
Weighted average basic and diluted common shares outstanding	84,560	76,889	66,576	61,892	58,633
Balance Sheet Data:					
Cash and cash equivalents	$ 487,429	$ 495,072	$ 381,165	$ 162,591	$ 282,876
Total assets	$ 742,299	$ 604,556	$ 462,047	$ 237,956	$ 356,556
Total long-term liabilities	$ 395,385	$ 316,558	$ 56,332	$ 55,484	$ 22,599
Total shareholders' equity	$ 261,674	$ 208,266	$ 361,059	$ 154,483	$ 311,698

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) in September 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. Nontuberculous mycobacterial (NTM) lung disease caused by MAC (which we refer to as 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 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, France, Germany, Ireland, Italy, the Netherlands, the United Kingdom (UK), Switzerland, Japan and Bermuda.

Prior to 2019, we had not generated significant revenue and through December 31, 2019, we had an accumulated deficit of $1.5 billion. 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, 2019 will enable us to fund our operations for at least the next 12 months.

We expect to continue to incur operating losses at our US and certain international entities, as we plan to 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 increase of production capacity at Patheon and process improvements; 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.

APPROVED PRODUCT - ARIKAYCE

ARIKAYCE is our first approved product. Accelerated approval of ARIKAYCE was supported by preliminary data from the 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. In May 2019, we presented at the American Thoracic Society meeting that 41/65 (63.1%) of patients on ARIKAYCE plus GBT who had achieved culture conversion by Month 6 had maintained durable culture conversion for three months off all therapy compared to 0/10 (0%) on GBT only ($p<0.0002$). Safety data for these patients were consistent with safety data previously reported for patients by Month 6 of the CONVERT study.

Patients who did not culture convert by Month 6 may have been eligible to enroll in the 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 and final efficacy data regarding culture conversion were consistent with these interim data. We have analyzed the safety and efficacy data from the 312 study, and we did not observe any new safety signals.

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, will be designed 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. We have initiated efforts to evaluate an appropriate PRO tool through a short-term study to enable the assessment of therapies for the treatment of NTM lung disease. In parallel, we plan to begin a confirmatory clinical study of ARIKAYCE in a front-line setting of patients with MAC lung disease in the second half of 2020. We continue to collaborate with the FDA on the timetable as well as the design and validation of the PRO and the post-approval confirmatory clinical trial. The full approval of ARIKAYCE will be contingent upon verification and description of clinical benefit in the post-approval confirmatory study.

Further Research and Lifecycle Management

We are currently exploring and supporting research and lifecycle management programs for ARIKAYCE 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 study designs focusing on the MAC lung disease treatment pathway, including front-line treatment and maintenance to prevent recurrence (defined as true relapse or reinfection) of MAC lung disease. As noted above, in parallel, we plan to conduct our required confirmatory trial to assess and describe the clinical benefit of ARIKAYCE in patients with MAC lung disease beginning in the second half of 2020.

Subsequent lifecycle management studies could also potentially enable us to reach more patients. The use of ARIKAYCE to treat infections caused by non-MAC NTM species is being evaluated. For instance, we plan to conduct a study in patients with NTM lung disease caused by *M. abscessus*. These initiatives also 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.

PIPELINE PROGRESS

INS1007

INS1007 is a small molecule, oral, reversible inhibitor of DPP1, which we licensed from AstraZeneca in October 2016. We are developing INS1007 for the treatment of patients with bronchiectasis. DPP1 is an enzyme responsible for activating neutrophil serine proteases (NSPs) 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 NSPs (including neutrophil elastase (NE), 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 result in excessive active NSPs that cause lung destruction and inflammation. INS1007 may decrease the damaging effects of inflammatory diseases such as non-cystic fibrosis bronchiectasis (NCFBE) by inhibiting DPP1 and its activation of NSPs.

NCFBE is a severe, chronic pulmonary disorder in which the bronchi become permanently dilated due to a cycle of infection, inflammation, and lung tissue damage. The condition is marked by frequent pulmonary exacerbations requiring antibiotic therapy and/or hospitalizations. Symptoms include chronic cough, excessive sputum production, shortness of breath, and repeated respiratory infections, which can worsen the underlying condition. NCFBE affects approximately 340,000 to 520,000 patients in the US. Currently, there is no cure, and there are no approved therapies specifically targeting NCFBE in the US, Europe, or Japan. We are also exploring the potential of INS1007 in various neutrophil-driven inflammatory conditions.

As a result of the positive results of the WILLOW study discussed below, we plan to design and conduct a Phase 3 program, which will primarily investigate INS1007 in NCFBE. Based on indications from the FDA, we expect that the primary endpoint will be frequency of pulmonary exacerbation.

The WILLOW Study

The WILLOW study was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, multi-national, Phase 2 study to assess the efficacy, safety and tolerability, and pharmacokinetics of INS1007 administered once daily for 24 weeks in patients with NCFBE. The WILLOW study was conducted at 116 sites and enrolled 256 adult patients diagnosed with NCFBE who had at least two documented pulmonary exacerbations in the 12 months prior to screening. Patients were randomized 1:1:1 to receive either 10 mg or 25 mg of INS1007 or matching placebo. The primary efficacy endpoint was the time to first pulmonary exacerbation over the 24-week treatment period in the INS1007 arms compared to the placebo arm.

WILLOW Top-Line Efficacy Data

The top-line data demonstrates that the WILLOW study met its primary endpoint of time to first pulmonary exacerbation over the 24-week treatment period for both the 10 mg and 25 mg dosage groups of INS1007 compared to placebo ($p=0.027$, $p=0.044$, respectively). In addition, treatment with INS1007 resulted in a reduction in the frequency of pulmonary exacerbations, a key secondary endpoint, versus placebo. Specifically, patients treated with INS1007 experienced a 36% reduction in the 10 mg arm ($p=0.041$) and a 25% reduction in the 25 mg arm ($p=0.167$) versus placebo. Change in concentration of active NE in sputum versus placebo from baseline to the end of the treatment period was also statistically significant ($p=0.034$ for 10 mg, $p=0.021$ for 25 mg).

WILLOW Top-Line Safety and Tolerability Data

INS1007 was generally well-tolerated in the study. Rates of adverse events (AEs) leading to discontinuation in patients treated with placebo, INS1007 10 mg, and INS1007 25 mg were 10.6%, 7.4%, and 6.7%, respectively. The most common AEs in patients treated with INS1007 were cough, headache, sputum increase, dyspnea, fatigue, and upper respiratory tract infection. Rates of adverse events of special interest (AESIs) in patients treated with placebo, INS1007 10 mg, and INS1007 25 mg, respectively, were as follows: rates of periodontal disease were 2.4%, 7.4%, and 10.1%; rates of hyperkeratosis were 0%, 3.7%, and 1.1%; and rates of infections that were considered AESIs were 18.8%, 16.0%, and 16.9%.

Further Research

In August 2019, we received notice from the FDA that we were awarded a development grant of $1.8 million for specific work to be performed on a PRO tool over the next two years. The grant funding is for the development of a novel PRO tool for use in clinical trials to measure symptoms in patients with NCFBE with and without NTM lung infection.

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 advancing its development to a Phase 1 study 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 prompt pay discounts, service fees, estimated rebates, including government rebates, such as Medicaid rebates and Medicare Part D coverage gap reimbursements in the US, chargebacks and returns. We also began recognizing revenue related to early access programs (EAPs) in Europe, consisting of sales to the French National Agency for Medicines and Health Products Safety (ANSM), which has granted ARIKAYCE a Temporary Authorization for Use (Autorisation Temporaire d'Utilisation or ATU) and from the named patient program in Germany, both compassionate use programs.

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, and allocation of overhead costs, in addition to royalty expenses and revenue-based milestones. We began capitalizing inventory upon FDA approval of ARIKAYCE. All costs related to inventory for ARIKAYCE prior to FDA approval were expensed as incurred and therefore not included in cost of product revenues.

Research and Development (R&D) Expenses

R&D expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in our research and development functions, including medical affairs. R&D expense also includes other internal operating expenses, the cost of manufacturing a product candidate, including the medical devices for drug delivery, for clinical study, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. In addition, R&D expenses include payments to third parties for the license rights to products in development (prior to marketing approval), such as INS1007. Our R&D expenses related to manufacturing our product candidates and medical devices for clinical study are primarily related to activities at contract manufacturing organizations (CMOs) that manufacture INS1007 and INS1009. Our R&D expenses related to clinical trials are primarily related to activities at contract research organizations (CROs) that conduct

and manage clinical trials on our behalf. These contracts with CROs set forth the scope of work to be completed at a fixed fee or amount per patient enrolled. Payments under these contracts with CROs primarily depend on performance criteria such as the successful enrollment of patients or the completion of clinical trial milestones as well as time-based fees. Expenses are accrued based on contracted amounts applied to the level of patient enrollment and to activity according to the clinical trial protocol. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized. Such amounts are then recognized as an expense as the related goods are delivered or the services are performed, or when the goods or services are no longer expected to be provided.

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 commercial activities, insurance, board of director fees, tax and accounting services and certain milestones related to ARIKAYCE.

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, 2019 and 2018

Overview - Operating Results

Our operating results for the year ended December 31, 2019, included the following:

- Total revenues from sales of ARIKAYCE increased $126.6 million as compared to the prior year as a result of the launch of ARIKAYCE in the fourth quarter of 2018;
- Cost of product revenues (excluding amortization of intangibles) increased $21.8 million as compared to the prior year as a result of the launch of ARIKAYCE in the fourth quarter of 2018;
- R&D expenses decreased $13.6 million as compared to the prior year primarily resulting from costs relating to the Patheon production facility being included in other assets in 2019 and external manufacturing expenses for ARIKAYCE being included as a component of inventory in 2019;
- SG&A expenses increased $42.6 million as compared to the prior year resulting from external expenses related to ARIKAYCE and the Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) milestone;
- Amortization of intangible assets increased $3.7 million as compared to the prior year; and
- Interest expense increased $2.2 million as compared to the prior year related primarily to the accretion of the debt discount on the $450.0 million aggregate principal amount of 1.75% convertible senior notes due 2025 (the Convertible Notes).

Net loss for the year ended December 31, 2019 was $254.3 million, or $3.01 per share—basic and diluted, compared with a net loss of $324.3 million, or $4.22 per share—basic and diluted, for the year ended December 31, 2018.

Revenues

Total revenue consists of net sales of ARIKAYCE, which was approved by the FDA in September 2018 and launched in the US in October 2018. The following table summarizes the sources of revenue for the years ended December 31, 2019 and 2018 (in thousands):

	For the Year Ended December 31,		Increase (decrease)	
	2019	2018	$	%
Net product revenues, US	$ 132,094	$ 9,265	$ 122,829	1326%
Net product revenues, EAPs	4,373	570	3,803	667%
Total revenues	$ 136,467	$ 9,835	$ 126,632	1288%

Revenues for the year ended December 31, 2019 increased to $136.5 million as compared to $9.8 million in 2018. The increase was a result of having a full year of ARIKAYCE sales in 2019, after the launch of ARIKAYCE in the fourth quarter of 2018.

Cost of Product Revenues (excluding amortization of intangibles)

Cost of produce revenues increased to $24.2 million for the year ended December 31, 2019 as compared to $2.4 million in 2018. All product costs incurred prior to FDA approval of ARIKAYCE in September 2018 were expensed as R&D expenses. Cost of product revenues (excluding amortization of intangibles) consists primarily of direct and indirect costs related to the manufacturing of ARIKAYCE sold, including third-party manufacturing costs, packages services, freight, and production-related overhead costs, in addition to royalty and revenue-based milestones. We expect our cost of product revenues (excluding amortization of intangibles) as a percent of revenue to increase in 2020.

R&D Expenses

R&D expenses for the years ended December 31, 2019 and 2018 were comprised of the following (in thousands):

	Years Ended December 31,		Increase (decrease)	
	2019	2018	$	%
External Expenses				
Clinical development and research	$ 32,421	$ 30,287	$ 2,134	7.0%
Manufacturing	10,416	43,824	(33,408)	(76.2)%
Regulatory, quality assurance, and medical affairs	13,343	12,290	1,053	8.6%
Subtotal—external expenses	$ 56,180	$ 86,401	$ (30,221)	(35.0)%
Internal Expenses				
Compensation and benefit related expenses	$ 53,535	$ 38,794	$ 14,741	38.0%
Stock-based compensation	8,210	9,395	(1,185)	(12.6)%
Other internal operating expenses	13,786	10,693	3,093	28.9%
Subtotal—internal expenses	$ 75,531	$ 58,882	$ 16,649	28.3%
Total	$ 131,711	$ 145,283	$ (13,572)	(9.3)%

R&D expenses decreased to $131.7 million during the year ended December 31, 2019 from $145.3 million in 2018. The $13.6 million decrease was primarily due to a decrease of $33.4 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 costs relating to increasing our long-term production capacity at Patheon. This was partially offset by a $14.7 million increase in compensation and related expenses due to an increase in headcount in the year ended December 31, 2019 as compared to the prior year.

During the year ended December 31, 2019, external R&D expenses of $56.2 million consisted of $29.0 million related to ARIKAYCE, $22.0 million related to INS1007, and $5.2 million related to other research expenses. 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.

SG&A Expenses

SG&A expenses for the years ended December 31, 2019 and 2018 were comprised of the following (in thousands):

	Years Ended December 31,		Increase (decrease)	
	2019	2018	$	%
Compensation and benefit related expenses	$ 67,064	$ 62,592	$ 4,472	7.1 %
Stock-based compensation	18,761	16,845	1,916	11.4 %
Professional fees and other external expenses	97,855	70,248	27,607	39.3 %
Facility related and other internal expenses	27,116	18,533	8,583	46.3 %
Total SG&A expenses	$ 210,796	$ 168,218	$ 42,578	25.3 %

SG&A expenses increased to $210.8 million during the year ended December 31, 2019 from $168.2 million in 2018. The $42.6 million increase was primarily due to a $27.6 million increase in professional fees and other external expenses related to ARIKAYCE, including disease awareness efforts, patient support activities, field operations, and other professional fees. SG&A for the year ended December 31, 2019 included approximately $10.2 million for a certain milestone related to the CFFT agreements. SG&A also increased $8.6 million due to higher facility related and other internal expenses.

Amortization of Intangible Assets

Amortization of intangible assets for the years ended December 31, 2019 and 2018 was $5.0 million and $1.2 million, respectively. Amortization of intangible assets 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 $27.7 million for the year ended December 31, 2019 as compared to $25.5 million for 2018. The $2.2 million increase in interest expense in the year ended December 31, 2019 as compared to the prior year period relates to accretion of the debt discount on the $450.0 million aggregate principal amount of Convertible Notes. The interest expense on the Convertible Notes is based on an effective interest rate of 7.6%.

Provision (benefit) for Income Taxes

The income tax provision was $0.8 million and $0.2 million for the years ended December 31, 2019 and 2018, respectively. The income tax provision for the year ended December 31, 2019 and 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.

Comparison of the Years Ended December 31, 2018 and 2017

Please refer to the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" in our Annual Report on Form 10-K for the fiscal year ended December 31, 2018 for a comparative discussion of our fiscal years ended December 31, 2018 and December 31, 2017.

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. We expect to continue to incur operating losses at our US and certain international entities, as we plan to fund R&D for ARIKAYCE and our other pipeline programs, continue commercialization activities for ARIKAYCE in the US, continue to invest in pre-commercial and regulatory activities for ARIKAYCE in Europe and Japan, and other general and administrative activities.

In the second quarter of 2019, we completed an underwritten public offering of 10,657,692 shares of common stock, which included the underwriters' exercise in full of its over-allotment option of 1,042,307 shares from the Company at a price to the public of $26.00, less underwriting discounts. Our net proceeds from the sale of the shares, after deducting underwriting discounts and commissions and other offering expenses of $16.0 million, were $261.1 million. The offering also included the sale of 400,000 shares from our Chairman and Chief Executive Officer, from which we received no proceeds.

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 other offering expenses of $24.8 million, were $377.7 million.

We may need to raise additional capital to fund our operations, including continued commercialization of ARIKAYCE and future clinical trials related to ARIKAYCE, to design and conduct a Phase 3 program for INS1007, to develop INS1009, and to develop, acquire, in-license or co-promote other products or product candidates, including those 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 expect to opportunistically raise additional capital and may do so 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 and product candidates. During 2020, we plan to support the commercialization of ARIKAYCE in the US, to continue to fund further clinical development of ARIKAYCE and INS1007, and to fund our global expansion efforts to support pre-commercial activities in Europe and Japan including obtaining regulatory approvals for ARIKAYCE in those regions. Our cash requirements for the next 12 months will be impacted by a number of factors, the most significant of which we expect to be expenses related to the commercialization efforts for ARIKAYCE, expenses related to the development activities for INS1007, and to a lesser extent, future ARIKAYCE clinical trials.

Cash Flows

As of December 31, 2019, we had cash and cash equivalents of $487.4 million, as compared with $495.1 million as of December 31, 2018. The $7.6 million decrease was due to cash used in operating activities and, to a lesser extent, cash used in investing activities, mostly offset by cash received from the underwritten public offering of our common stock in the second quarter of 2019. Our working capital was $470.0 million as of December 31, 2019 as compared with $439.2 million as of December 31, 2018.

Net cash used in operating activities was $250.6 million and $258.0 million for the years ended December 31, 2019 and 2018, respectively. The net cash used in operating activities during the years ended December 31, 2019 and 2018 was primarily for the commercial 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, 2019 and 2018 included clinical trial expenses related to INS1007.

Net cash used in investing activities was $42.3 million and $14.8 million for the years ended December 31, 2019 and 2018, respectively. The net cash used in investing activities during 2019 was primarily related to the investment in our long-term production capacity at Patheon and our new corporate headquarters. The net cash used in investing activities during 2018 was primarily related to the investment in our long-term production capacity at Patheon. We expect our net cash used in investing activities will decrease in 2020 as compared to 2019 as a result of the completion of our corporate headquarters and the remaining investment required at the Patheon facility.

Net cash provided by financing activities was $285.3 million and $386.7 million for the years ended December 31, 2019 and 2018, respectively. Net cash provided by financing activities for the year ended December 31, 2019 included net cash proceeds of $261.1 million from our underwritten public offering of 10,657,692 shares in the second quarter of 2019 and cash proceeds from stock option exercises. Net cash provided by financing activities during 2018 included net cash proceeds of $435.8 million from our convertible debt issuance and cash proceeds received from stock option exercises.

Contractual Obligations

In January 2018, we completed an underwritten public offering of $450.0 million aggregate principal amount of Convertible Notes pursuant to an indenture between the Company and Wells Fargo Bank, National Association, as trustee. Our net proceeds from the offering, after deducting underwriting discounts and commissions and other offering expenses of $14.2 million, were approximately $435.8 million. The Convertible Notes bear interest payable semiannually in arrears on January 15 and July 15 of each year, beginning on July 15, 2018. The Convertible Notes mature on January 15, 2025, unless earlier converted, redeemed, or repurchased. The Convertible Notes are convertible into common stock of the Company under certain circumstances described in the indenture. For more information, see *Note 8 - Debt* in our notes to the consolidated financial statements.

In September 2018, we entered into an agreement (the Lease) with Exeter 700 Route 202/206, LLC to lease 117,022 square feet of office space located in Bridgewater, New Jersey for our corporate headquarters. Subject to certain conditions, we have the one-time option to expand the leased premises by up to 50,000 rentable square feet, exercisable prior to the fifth

anniversary of the Commencement Date, which was October 1, 2019. The initial Lease term runs 130 months from the Commencement Date and we have the option to extend that term for up to three additional five-year periods. In addition, we are responsible for operating expenses and taxes pursuant to the Lease. Future minimum payments under the Lease during the initial Lease Term are approximately $32.3 million. The Lease contains customary default provisions, including those relating to payment defaults, performance defaults and events of bankruptcy.

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 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. Under the agreement, we are obligated to pay certain minimum amounts for the batches of ARIKAYCE produced each calendar year.

In September 2015, we entered into a Commercial Fill/Finish Services Agreement (the Fill/Finish Agreement) with Althea, for Althea to produce, on a non-exclusive basis, ARIKAYCE in finished dosage form at a 50 kg scale. Under the Fill/Finish Agreement, we are obligated to pay a minimum of $2.7 million for the batches of ARIKAYCE produced 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, the agreement remains 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 a licensing agreement with PARI for the use of the optimized Lamira Nebulizer System for delivery of ARIKAYCE in treating patients with NTM lung infections, 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 the system with ARIKAYCE for the treatment of such indications, but we cannot manufacture the nebulizers except as permitted under our Commercialization Agreement with PARI, as described below. The Lamira Nebulizer System has been approved for use in the US (in combination with ARIKAYCE) and the EU. Under the licensing agreement, we made an upfront license fee and milestone payments to PARI. Upon FDA acceptance of our New Drug Application and the subsequent FDA approval of ARIKAYCE, we made additional milestone payments of €1.0 million and €1.5 million, respectively, to PARI. In addition, PARI is entitled to receive a future milestone payment of €0.5 million in cash based on receipt of the first 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, which was included within selling, general and administrative expenses in the fourth quarter of 2017. 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.

In July 2014, we entered into a Commercialization Agreement with PARI for the manufacture and supply of the 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 the Company 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 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.

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 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 aggregate investment to increase our long-term production capacity, 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.

In 2004 and 2009, we entered into research funding agreements with CFFT whereby we received $1.7 million and $2.2 million in research funding for the development of ARIKAYCE. As a result of the US approval of ARIKAYCE and in accordance with the agreements, as amended, we owe milestone payments to CFFT of $13.4 million in the aggregate, which are payable through 2025. In addition, if certain global sales milestones are met within five years of ARIKAYCE's

commercialization, we will owe additional payments of up to $3.9 million. We have estimated the likelihood of meeting such global sales milestones and have accrued for these contingent obligations proportionally based on net sales of ARIKAYCE.

As of December 31, 2019, future payments under our long-term debt agreements, minimum future payments under non-cancellable leases and minimum future payment obligations are as follows (in thousands):

		As of December 31, 2019 Payments Due By Period			
	Total	Less than 1 year	1 - 3 Years	3 - 5 Years	More than 5 Years
Debt obligations					
Debt maturities	$ 450,000	$ —	$ —	$ —	$ 450,000
Contractual interest	43,334	7,875	15,750	15,750	3,959
Capital leases	32,250	2,939	5,276	5,252	18,783
Operating leases	3,521	1,926	1,595	—	—
Purchase obligations	82,017	10,767	11,850	9,450	49,950
CFFT milestone payments	13,400	1,000	3,900	5,500	3,000
Total contractual obligations	$ 624,522	$ 24,507	$ 38,371	$ 35,952	$ 525,692

This table does not include: (a) any milestone payments, except for the CFFT milestone payments included in the table above, which may become payable to third parties under our license and collaboration agreements as the timing and likelihood of such payments are not known; (b) the royalty payments specified below, as the amounts of such payments, timing and/or the likelihood of such payments are not known; (c) contracts that are entered into in the ordinary course of business which are not material in the aggregate in any period presented above; and (d) any payments related to the agreements mentioned below.

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 $23 million over the period of the study.

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 (which we renamed INS1007). In consideration of the licenses and other rights granted by AstraZeneca, we made an upfront payment of $30.0 million, which was included as research and development expense in the fourth quarter of 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. The next contingent milestone payment to AstraZeneca is $12.5 million and is due upon first dosing in a Phase 3 study. 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 any 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.

Future Funding Requirements

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, including those that address orphan or rare diseases. We expect that our future capital requirements may be substantial and will depend on many factors, including:

- The timing and cost of our future clinical trials of ARIKAYCE for the treatment of patients with NTM lung infections;
- The decisions of the EMA, MHLW and PMDA with respect to our applications for marketing approval of ARIKAYCE in Europe and Japan;
- The costs of activities related to the regulatory approval process and the timing of approvals, if received;

- The cost of supporting the sales and marketing efforts necessary to support the continued commercial efforts of ARIKAYCE;
- The cost of filing, prosecuting, defending, and enforcing patent claims;
- The timing and cost of our anticipated clinical trials, including our planned INS1007 Phase 3 program and the related milestone payments due to AstraZeneca;
- The costs of our manufacturing-related activities;
- The costs associated with commercializing ARIKAYCE outside the US, if approved; and
- The levels, timing and collection of revenue earned from sales of ARIKAYCE and other products approved in the future, if any.

We have raised $1.1 billion in net proceeds from securities offerings since September 2017. We believe we currently have sufficient funds to meet our financial needs for at least the next 12 months. However, our business strategy may require us to raise additional capital at any time through equity or debt financing(s), strategic transactions or otherwise.

Off-Balance Sheet Arrangements

We do not have any off-balance sheet arrangements that have or are reasonably likely to have a current or future material effect on our financial condition, revenues or expenses, results of operations, liquidity, capital expenditures or capital resources. We do not have any interest in special purpose entities, structured finance entities or other variable interest entities.

CRITICAL ACCOUNTING POLICIES

Preparation of financial statements in accordance with generally accepted accounting principles in the US requires us to make estimates and assumptions affecting the reported amounts of assets, liabilities, revenues and expenses and the disclosures of contingent assets and liabilities. We use our historical experience and other relevant factors when developing our estimates and assumptions and we regularly evaluate these estimates and assumptions. The amounts of assets and liabilities reported in our consolidated balance sheets and the amounts reported in our consolidated statements of comprehensive loss are affected by estimates and assumptions, which are used for, but not limited to, the accounting for revenue recognition, research and development, stock-based compensation, inventory, finite-lived intangible assets, and accrued expenses. The accounting policy discussed below is considered critical to an understanding of our consolidated financial statements because its application involves the most significant judgment. Actual results could differ materially from our estimates. For additional accounting policies, see Note 2 to our Consolidated Financial Statements—*Summary of Significant Accounting Policies.*

Revenue Recognition

Product revenues consist primarily of 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. Product revenues are recognized for arrangements within the scope of ASC 606, once we perform the following five steps: (1) identify the contracts with a customer; (2) identify the performance obligations in the contract; (3) determine the transaction price; (4) allocate the transaction price to the performance obligations in the contract; and (5) recognize revenue when or as the entity satisfies a performance obligation.

Revenue is recorded at net selling price (transaction price), which includes estimates of variable consideration for which reserves are established for (a) customer payments, such as invoice discounts for prompt pay and specialty pharmacies fees, (b) estimated government rebates, such as Medicaid and Medicare Part D reimbursements, and estimated managed care rebates, (c) estimated chargebacks, and (d) estimated costs of co-payment assistance. These reserves are based on the amounts earned or to be claimed on the related sales and are classified as reductions of accounts receivable (prompt pay discounts and chargebacks), prepaid expenses (co-payment assistance), or as a current liability (customer fees and rebates). Where appropriate, these estimates take into consideration a range of possible outcomes which are probability-weighted for relevant factors such as our historical experience, current contractual and statutory requirements, and forecasted customer buying and payment patterns. Overall, these reserves reflect our best estimates of the amount of consideration to which the relevant third party is entitled based on the terms of the applicable contract. The amount of variable consideration included in the transaction price may be constrained and is included in the net sales price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from our estimates, we adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

Customer payments: Our customers are offered various forms of consideration, including fees for enhanced services and prompt payment discounts. The payment terms for sales to specialty pharmacies for prompt payment discounts and fees for services are based on contractual rates agreed with the respective specialty pharmacies. We anticipate that our customers will earn these discounts and fees and, therefore, we deduct the full amount of these discounts and fees from total gross product

revenues at the time such revenues are recognized.

Rebates: We contract with government agencies and managed care organizations, or collectively, third-party payors, so that ARIKAYCE will be eligible for purchase by, or partial or full reimbursement from, such third-party payors. We estimate the rebates we will provide to third-party payors and deduct these estimated amounts from total gross product revenues at the time the revenues are recognized. These reserves are recorded in the same period in which the revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability, which is included in accrued expenses on the consolidated balance sheets. We estimate the rebates that will be provided to third-party payors based upon (i) our contracts with these third-party payors, (ii) the government mandated discounts applicable to government-funded programs, (iii) a range of possible outcomes that are probability-weighted for the estimated payor mix, and (iv) information obtained from our specialty pharmacies.

Chargebacks: Chargebacks are discounts that occur when certain contracted customers, currently public health service institutions and federal government entities purchasing via the Federal Supply Schedule, purchase directly from our specialty distributor. Contracted customers generally purchase the product at a discounted price and the specialty distributor, in turn, charges back to us the difference between the price they initially paid and the discounted price paid by the contracted customers. We estimate the chargebacks provided to the specialty distributor and deduct these estimated amounts from gross product revenues at the time revenues are recognized.

Co-payment assistance: Patients who have commercial insurance and meet certain eligibility requirements may receive co-payment assistance. Based upon the terms of the program and our historical experience with copay redemptions, we estimate the average co-pay mitigation amounts and the percentage of patients that we expect to participate in the program in order to establish our accruals for co-payment assistance. These reserves are recorded in the same period in which the related revenue is recognized, resulting in a reduction of product revenue. We adjust our accruals for co-pay assistance based on actual redemption activity and estimates of future redemptions related to sales in the current period.

If any, or all, of our actual experience vary from the estimates above, we may need to adjust prior period accruals, affecting revenue in the period of adjustment.

We also began recognizing revenue related to early access programs (EAPs) in Europe, consisting of sales to the French National Agency for Medicines and Health Products Safety, which granted ARIKAYCE a Temporary Authorization for Use (Autorisation Temporaire d'Utilisation or ATU) and from the named patient program in Germany, both compassionate use programs. EAPs are intended to make products available on a named patient basis before they are commercially available in accordance with local regulations.

Recent Accounting Pronouncements—Adopted

Topic 842 was effective for fiscal years beginning after December 15, 2018 (including interim periods within those years) and early adoption was permitted. In August 2018, the FASB issued ASU 2018-11, *Targeted Improvements to ASC 842*, which provided a transition option in which an entity would initially apply ASU 2016-02 at the adoption date and recognize a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption. We used the new transition option and the package of practical expedients that allowed it to not reassess: (1) whether any expired or existing contracts are or contain leases; (2) lease classification for any expired or existing leases; and (3) initial direct costs for any expired or existing leases. We also used the practical expedient that allows us to treat the lease and non-lease components of our leases as a single component. We adopted ASU 2016-02 effective January 1, 2019. The impact of the adoption of ASU 2016-02 on the consolidated balance sheet was $47.4 million.

In August 2016, the FASB issued ASU 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments*, which addressed eight specific cash flow issues with the objective of reducing the existing diversity in practice. Among the updates, the standard requires debt extinguishment costs to be classified as cash outflows for financing activities. This standard update became effective as of the first quarter of 2018. As a result of the adoption of the standard, in the first quarter of 2018, we reported a $2.2 million loss on extinguishment of debt in the operating activities section of its consolidated statement of cash flows. We had no material debt extinguishment costs prior to the first quarter of 2018. The impact of adopting this standard was not material to us.

Recent Accounting Pronouncements—Not Yet Adopted

In June 2016, the FASB issued ASU 2016-13, Financial Instruments - Credit Losses which requires financial assets measured at an amortized cost basis to be presented at the net amount expected to be collected. The measurement of expected credit losses is based on relevant information about past events, including historical experience, current conditions, and reasonable and supportable forecasts that affect the collectability of the reported amount. ASU 2016-13 is effective for fiscal years beginning after December 15, 2019 and we will adopt the standard effective January 1, 2020. Different aspects of the

guidance require modified retrospective or prospective adoption. We have performed an assessment and determined that adoption will not have a material impact on our consolidated financial statements.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

As of December 31, 2019, our cash and cash equivalents were in cash accounts or were invested in US treasury bills and money market funds. Our investments in US treasury bills and money market funds are not insured by the federal government.

As of December 31, 2019, we had $450.0 million of Convertible Notes outstanding which bear interest at a coupon rate of 1.75%. If a 10% change in interest rates had occurred on December 31, 2019, it would not have had a material effect on the fair value of our debt as of that date, nor would it have had a material effect on our future earnings or cash flows.

The majority of our business is conducted in US dollars. However, we do conduct certain transactions in other currencies, including Euros, British Pounds and Japanese Yen. Historically, fluctuations in foreign currency exchange rates have not materially affected our results of operations. During the years ended December 31, 2019, 2018 and 2017, our results of operations were not materially affected by fluctuations in foreign currency exchange rates.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The information required by Item 8 is included in our Financial Statements and Supplementary Data set forth in Item 15 of Part IV of this Annual Report on Form 10-K.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

Our management, under the supervision and with the participation of our Chief Executive Officer and Chief Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2019. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d- 15(e) under the Securities Exchange Act of 1934, as amended (the Exchange Act) means controls and other procedures that are designed to ensure that information required to be disclosed by us in the reports that we file or submit with the SEC is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms, and to ensure that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. Based on that evaluation our Chief Executive Officer and Chief Financial Officer have concluded that our disclosure controls and procedures were effective as of December 31, 2019 at the reasonable assurance level.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rule 13a-15(f) and 15d-15(f) under the Exchange Act, as a process designed by, or under the supervision of, our principal executive and principal financial and accounting officers and effected by our board of directors and management to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with US generally accepted accounting principles, and that receipts and expenditures of our company are being made only in accordance with authorizations of our management and board of directors; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risks that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2019, based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control—

Integrated Framework. Based on management's assessment, management concluded that the Company's internal control over financial reporting was effective as of December 31, 2019.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2019 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Attestation Report on Internal Control over Financial Reporting

Ernst & Young LLP, our independent registered public accounting firm, issued an attestation report on our internal control over financial reporting. The report of Ernst & Young LLP is contained in Item 15 of Part IV of this Annual Report on Form 10-K.

ITEM 9B. OTHER INFORMATION

None

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by Item 10 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Election of Class II Directors, Corporate Governance* and Delinquent *Section 16(a) Reports* in our definitive proxy statement for our 2020 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by Item 11 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Compensation Discussion and Analysis*, *Compensation Committee Report*, *Compensation Committee Interlocks and Insider Participation* and *Director Compensation* in our definitive proxy statement for our 2020 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by Item 12 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Compensation Discussion and Analysis*, *Security Ownership of Certain Beneficial Owners and Directors and Management* in our definitive proxy statement for our 2020 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS AND DIRECTOR INDEPENDENCE

The information required by Item 13 of Form 10-K is incorporated by reference from the discussion responsive thereto under the captions *Corporate Governance* and *Certain Relationships and Related Transactions* in our definitive proxy statement for our 2020 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report on Form 10-K.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by Item 14 of Form 10-K is incorporated by reference from the discussion responsive thereto under the caption *Corporate Governance* and *Ratification of the Appointment of Independent Registered Public Accounting Firm* in our definitive proxy statement for our 2020 annual meeting of shareholders to be filed with the SEC no later than 120 days after the close of the fiscal year covered by this Annual Report on Form 10-K.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) Documents filed as part of this report.

1. FINANCIAL STATEMENTS. The following consolidated financial statements of the Company are set forth herein, beginning on page 76:

(i) Reports of Independent Registered Public Accounting Firm

(ii) Consolidated Balance Sheets as of December 31, 2019 and 2018

(iii) Consolidated Statements of Comprehensive Loss for the Years Ended December 31, 2019, 2018 and 2017

(iv) Consolidated Statements of Shareholders' Equity for the Years Ended December 31, 2019, 2018 and 2017

(v) Consolidated Statements of Cash Flows for the Years Ended December 31, 2019, 2018 and 2017

(vi) Notes to Consolidated Financial Statements

2. FINANCIAL STATEMENT SCHEDULES.

None required.

3. EXHIBITS.

The exhibits that are required to be filed or incorporated by reference herein are listed in the Exhibit Index.

EXHIBIT INDEX

3.1	Articles of Incorporation of Insmed Incorporated, as amended through June 14, 2012 (incorporated by reference from Exhibit 3.1 to Insmed Incorporated's Annual Report on Form 10-K filed on March 18, 2013).
3.2	Amended and Restated Bylaws of Insmed Incorporated (incorporated by reference from Exhibit 3.1 to Insmed Incorporated's Quarterly Report on Form 10-Q filed on August 6, 2015).
4.1	Specimen stock certificate representing common stock, $0.01 par value per share, of the Registrant (incorporated by reference from Exhibit 4.2 to Insmed Incorporated's Registration Statement on Form S-4/A (Registration No. 333-30098) filed on March 24, 2000).
4.2	Indenture, dated as of January 26, 2018, by and between the Company and Wells Fargo Bank, National Association (incorporated by reference from Exhibit 4.1 to Insmed Incorporated’s Current Report on Form 8-K filed on January 26, 2018).
4.3	First Supplemental Indenture, dated as of January 26, 2018, by and between the Company and Wells Fargo Bank, National Association (incorporated by reference from Exhibit 4.2 to Insmed Incorporated’s Current Report on Form 8-K filed on January 26, 2018).
4.4	Form of 1.75% Convertible Senior Note due 2025 (included in Exhibit 4.3).
4.5	Description of Securities Registered Under Section 12 of the Securities Exchange Act of 1934 (filed herewith).
10.1**	Insmed Incorporated Amended and Restated 2000 Stock Incentive Plan (incorporated by reference from Exhibit 10.3 to Insmed Incorporated's Form 10-Q filed on May 8, 2013).
10.2**	Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 99.1 to Insmed Incorporated's Registration Statement on Form S-8 filed on May 24, 2013).
10.2.1**	Form of Award Agreement for Incentive Stock Options pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.5 to Insmed Incorporated's Annual Report on Form 10-K filed on March 6, 2014).

10.2.2**	Form of Award Agreement for Non-Qualified Stock Options pursuant to the Insmed Incorporated 2013 Incentive Plan (incorporated by reference from Exhibit 10.6 to Insmed Incorporated's Annual Report on Form 10-K filed on March 6, 2014).
10.3**	Insmed Incorporated 2015 Incentive Plan (incorporated by reference from Exhibit 99.1 to Insmed Incorporated's Registration Statement on Form S-8 filed on May 28, 2015).
10.3.1**	Form of Award Agreement for Non-Qualified Stock Options pursuant to the Insmed Incorporated 2015 Incentive Plan (incorporated by reference from Exhibit 10.2 to Insmed Incorporated’s Form 10-Q filed May 3, 2017).
10.4**	Insmed Incorporated 2017 Incentive Plan (incorporated by reference from Exhibit 10.3 to Insmed Incorporated’s Form 10-Q filed August 3, 2017).
10.4.1**	Form of Award Agreements for Restricted Stock Units pursuant to the Insmed Incorporated 2017 Incentive Plan (incorporated by reference from Exhibit 10.4 to Insmed Incorporated’s Form 10-Q filed August 3, 2017).
10.4.2**	Form of Award Agreement for Non-Qualified Stock Options pursuant to the Insmed Incorporated 2017 Incentive Plan (incorporated by reference from Exhibit 10.5 to Insmed Incorporated’s Form 10-Q filed August 3, 2017).
10.5**	Insmed Incorporated 2019 Incentive Plan (incorporated by reference from Exhibit 10.1 to Insmed Incorporated’s Form 10-Q filed August 1, 2019).
10.5.1**	Form of Award Agreement for Restricted Stock Units pursuant to the Insmed Incorporated 2019 Incentive Plan (incorporated by reference from Exhibit 10.2 to Insmed Incorporated’s Form 10-Q filed August 1, 2019).
10.5.2**	Form of Award Agreement for Non-Qualified Stock Options pursuant to the Insmed Incorporated 2019 Incentive Plan (incorporated by reference from Exhibit 10.3 to Insmed Incorporated’s Form 10-Q filed August 1, 2019).
10.5.3**	Form of Award Agreement for Restricted Stock Units issued to directors pursuant to the Insmed Incorporated 2019 Incentive Plan (incorporated by reference from Exhibit 10.4 to Insmed Incorporated’s Form 10-Q filed August 1, 2019).
10.6**	Insmed Incorporated Senior Executive Bonus Plan (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on November 5, 2013).
10.7**	Form of Non-Qualified Stock Option Inducement Award Agreement (incorporated by reference from Exhibit 10.6 to Insmed Incorporated’s Form 10-Q filed August 3, 2017).
10.8**	Form of Indemnification Agreement entered into with each of the Company's directors and officers (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on January 16, 2014).
10.9**	Employment Agreement, effective as of September 10, 2012, between Insmed Incorporated and William Lewis (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on September 11, 2012).
10.9.1**	Amendment to Employment Agreement, effective as of July 31, 2019, between Insmed Incorporated and William Lewis (incorporated by reference from Exhibit 10.5 to Insmed Incorporated’s Form 10-Q filed on August 1, 2019).
10.10**	Employment Agreement, effective as of July 29, 2013, between Insmed Incorporated and Christine Pellizzari (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on November 5, 2013).
10.10.1**	Amendment to Employment Agreement, effective as of September 26, 2016, between Insmed Incorporated and Christine Pellizzari (incorporated by reference from Exhibit 10.31 to Insmed Incorporated’s Annual Report on Form 10-K filed February 23, 2017).

10.10.2**	Second Amendment to Employment Agreement, effective as of July 31, 2019, between Insmed Incorporated and Christine Pellizzari (incorporated by reference from Exhibit 10.7 to Insmed Incorporated's Form 10-Q filed on August 1, 2019).
10.11**	Employment Agreement, effective as of January 2, 2013, between Insmed Incorporated and S. Nicole Schaeffer (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on May 7, 2015).
10.11.1**	Amendment to Employment Agreement, effective as of September 26, 2016, between Insmed Incorporated and S. Nicole Schaeffer (incorporated by reference from Exhibit 10.32 to Insmed Incorporated's Annual Report on Form 10-K filed February 23, 2017).
10.12**	Employment Agreement, effective as of September 27, 2016, between Insmed Incorporated and Roger Adsett (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed November 3, 2016).
10.12.1**	Amendment to Employment Agreement, effective as of July 31, 2019, between Insmed Incorporated and Roger Adsett (incorporated by reference from Exhibit 10.6 to Insmed Incorporated's Form 10-Q filed August 1, 2019).
10.13**	Employment Agreement, effective as of January 28, 2020, between Insmed Incorporated and Sara Bonstein (filed herewith).
10.14**	Employment Agreement, effective as of March 17, 2014, between Insmed Incorporated and John Goll (filed herewith).
10.15*	Employment Agreement, effective as of June 1, 2017, between Insmed Incorporated and Paolo Tombesi (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed August 3, 2017).
10.15.1*	Separation Agreement and General Release, effective as of May 3, 2019, between Insmed Incorporated and Paolo Tombesi (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 8-K filed on May 7, 2019).
10.16*	License Agreement, dated April 25, 2008, between Transave, Inc. and PARI Pharma GmbH, and Amendments No. 1-4 thereto (incorporated by reference from Exhibit 10.22 to Insmed Incorporated's Annual Report on Form 10-K filed on March 18, 2013).
10.16.1*	Amendment No. 5 to License Agreement between Insmed Incorporated and PARI Pharma GmbH, effective as of October 5, 2015 (incorporated by reference from Exhibit 10.14.1 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.16.2*	Amendment No. 6 to License Agreement between Insmed Incorporated and PARI Pharma GmbH, effective as of October 9, 2015 (incorporated by reference from Exhibit 10.14.2 to Insmed Incorporated's Annual Report on Form 10-K filed on February 25, 2016).
10.16.3*	Amendment No. 7 to License Agreement between Insmed Incorporated and PARI Pharma GmbH, effective as of July 21, 2017 (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on November 2, 2017).
10.16.4*	Amendment No. 8 to License Agreement between Insmed Incorporated and PARI Pharma GmbH, effective as of December 19, 2018 (incorporated by reference from Exhibit 10.15.4 to Insmed Incorporated's Annual Report on Form 10-K filed on February 22, 2019).
10.17*	Contract Manufacturing Agreement, dated February 7, 2014, between Insmed Incorporated and Therapure Biopharma Inc. (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on May 8, 2014).
10.17.1*	Amending Agreement, dated March 13, 2014, between Insmed Incorporated and Therapure Biopharma Inc. (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on May 8, 2014).
10.18*	Commercialization Agreement dated July 8, 2014 between Insmed Incorporated and PARI Pharma GmbH (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed on November 6, 2014).

10.18.1*	Amendment No. 1 to Commercialization Agreement between Insmed Incorporated and PARI Pharma GmbH, effective as of July 21, 2017 (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed on November 2, 2017).
10.19*	Master Agreement for Services, dated as of August 27, 2014, by and between Insmed Incorporated and SynteractHCR, Inc. (incorporated by reference from Exhibit 10.29 to Insmed Incorporated's Annual Report on Form 10-K filed on February 27, 2015).
10.19.1*	Work Order 1, dated as of December 30, 2014, by and between Insmed Incorporated and SynteractHCR, Inc. (incorporated by reference from Exhibit 10.30 to Insmed Incorporated's Annual Report on Form 10-K filed on February 27, 2015).
10.19.2*	Change in Scope 1 to Work Order 1, dated as of May 27, 2016, by and between Insmed Incorporated and SynteractHCR, Inc. (incorporated by reference from Exhibit 10.2 to Insmed Incorporated's Form 10-Q filed August 4, 2016).
10.20*	Commercial Fill/Finish Services Agreement between Insmed Incorporated and Ajinomoto Althea, Inc., dated as of September 15, 2015 (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed November 6, 2015).
10.20.1	Extension of Commercial Fill/Finish Services Agreement between Insmed Incorporated and Ajinomoto Althea, Inc., dated as of November 30, 2016 (incorporated by reference from Exhibit 10.30 to Insmed Incorporated's Annual Report on Form 10-K filed February 23, 2017).
10.20.2	Extension of Commercial Fill/Finish Services Agreement between Insmed Incorporated and Ajinomoto Althea, Inc., dated as of December 18, 2018 (incorporated by reference from Exhibit 10.29.2 to Insmed Incorporated's Annual Report on Form 10-K filed on February 22, 2019).
10.21*	Manufacturing and Supply Agreement between Insmed Incorporated and Patheon UK Limited, dated as of October 20, 2017 (incorporated by reference from Exhibit 10.39 to Insmed Incorporated's Annual Report on Form 10-K filed February 23, 2018).
10.22*	Technology Transfer Agreement between Insmed Incorporated and Patheon UK Limited, dated as of October 20, 2017 (incorporated by reference from Exhibit 10.40 to Insmed Incorporated's Annual Report on Form 10-K filed February 23, 2018).
10.23*	License Agreement, dated October 4, 2016, between Insmed Incorporated and AstraZeneca AB (incorporated by reference from Exhibit 10.29 to Insmed Incorporated's Annual Report on Form 10-K filed February 23, 2017).
10.24	Lease Agreement, effective as of July 1, 2016, by and between Insmed Incorporated and CIP II/AR Bridgewater Holdings, LLC (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Form 10-Q filed August 4, 2016).
10.25	Lease Agreement, dated September 11, 2018, by and between Insmed Incorporated and Exeter 700 Route 202/206, LLC (incorporated by reference from Exhibit 10.1 to Insmed Incorporated's Current Report on Form 8-K filed on September 17, 2018).
21.1	Subsidiaries of Insmed Incorporated (filed herewith).
23.1	Consent of Ernst & Young LLP (filed herewith).
31.1	Certification of William H. Lewis, Chairman and Chief Executive Officer (Principal Executive Officer) of Insmed Incorporated, pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes Oxley Act of 2003 (filed herewith).
31.2	Certification of Sara Bonstein, Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer) of Insmed Incorporated, pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes Oxley Act of 2003 (filed herewith).
32.1	Certification of William H. Lewis, Chairman and Chief Executive Officer (Principal Executive Officer) of Insmed Incorporated, pursuant to 18 USC Section 1350, as adopted pursuant to Section 906 of the Sarbanes Oxley Act of 2003 (filed herewith).
32.2	Certification of Sara Bonstein, Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer) of Insmed Incorporated, pursuant to 18 USC Section 1350, as adopted pursuant to Section 906 of the Sarbanes Oxley Act of 2003 (filed herewith).

101	The following materials from Insmed Incorporated's Annual Report on Form 10-K for the year ended December 31, 2019 formatted in iXBRL (Inline eXtensible Business Reporting Language): (i) Consolidated Balance Sheets as of December 31, 2019 and 2018, (ii) Consolidated Statements of Comprehensive Loss for the years ended December 31, 2019, 2018 and 2017, (iii) Consolidated Statements of Shareholders' Equity for the years ended December 31, 2019, 2018 and 2017, (iv) Consolidated Statements of Cash Flows for the years ended December 31, 2019, 2018, and 2017, and (v) Notes to the Consolidated Financial Statements, and (vi) Cover Page.
104	The cover page from the Annual Report on Form 10-K for the year ended December 31, 2019, formatted in iXBRL and contained in Exhibit 101.
*	Certain portions of this exhibit have been redacted.
**	Management contract or compensatory plan or arrangement.

ITEM 16. FORM 10-K SUMMARY

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized on February 25, 2020.

INSMED INCORPORATED
a Virginia corporation
(Registrant)

By: /s/ WILLIAM H. LEWIS
William H. Lewis
Chairman and Chief Executive Officer
(Principal Executive Officer)

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities indicated on February 25, 2020.

Signature	Title
/s/ WILLIAM H. LEWIS William H. Lewis	Chairman and Chief Executive Officer (Principal Executive Officer)
/s/ SARA BONSTEIN Sara Bonstein	Chief Financial Officer (Principal Financial and Accounting Officer)
/s/ DAVID R. BRENNAN David R. Brennan	Director
/s/ ALFRED F. ALTOMARI Alfred F. Altomari	Director
/s/ CLARISSA DESJARDINS, PH.D. Clarissa Desjardins, Ph.D.	Director
/s/ STEINAR J. ENGELSEN, M.D. Steinar J. Engelsen, M.D.	Director
/s/ DAVID W.J. MCGIRR David W.J. McGirr	Director
/s/ ELIZABETH MCKEE ANDERSON Elizabeth McKee Anderson	Director
/s/ MELVIN SHAROKY, M.D. Melvin Sharoky, M.D.	Director
/s/ LEO LEE Leo Lee	Director

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Insmed Incorporated

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Insmed Incorporated (the Company) as of December 31, 2019 and 2018, the related consolidated statements of comprehensive loss, shareholders' equity and cash flows for each of the three years in the period ended December 31, 2019, and the related notes (collectively referred to as the “consolidated financial statements”). In our opinion, the consolidated financial statements present fairly, in all material respects, the consolidated financial position of the Company at December 31, 2019 and 2018, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2019, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), and our report dated February 25, 2020 expressed an unqualified opinion thereon.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company’s financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Adoption of ASU No. 2016-02

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for leases in 2019 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, Leases (Topic 842), and the related amendments.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Variable consideration in contracts with customers

Description of the Matter	As discussed in Note 2 of the consolidated financial statements, the transaction price for product sales is typically adjusted for variable consideration, which includes rebates paid to government agencies. The Company estimates these reserves based upon a range of possible outcomes that are probability-weighted for the estimated payor mix. Auditing the Company's estimate of variable consideration for amounts to be paid to government agencies was complex and judgmental due to uncertainty about the ultimate third-party payor at the time of shipment to the specialty pharmacies and the amounts of rebates to be paid to those government agencies. In addition, government pricing calculations are complex as a result of assumptions about inputs such as the average manufacturer price, best price and the unit rebate amount. The transaction price is sensitive to these significant assumptions and calculations.
How We Addressed the Matter in Our Audit	We identified, evaluated and tested controls over management’s review of the calculated reductions to gross product prices related to government agencies including management's review of the significant assumptions and the data utilized in its calculations. To test the revenue adjustments related to government agencies our audit procedures included, among others, using internal specialists to assist with recalculating government pricing amounts that included inputs such as the average manufacturer price, best price and the unit rebate amount. We also tested the underlying data and inputs used by the Company in its determination of the estimated payor mix. We compared the inputs used by management to historical trends, evaluated the change in the estimated rebates amounts recorded throughout the year and assessed the historical accuracy of management's estimates against actual results.

/s/ Ernst & Young LLP

We have served as the Company’s auditor since at least 1999, but we are unable to determine the specific year.

Iselin, New Jersey
February 25, 2020

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Insmed Incorporated

Opinion on Internal Control over Financial Reporting

We have audited Insmed Incorporated's internal control over financial reporting as of December 31, 2019, based on criteria established in Internal Control - Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Insmed Incorporated (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2019, based on the COSO criteria**.**

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2019 and 2018, and the related consolidated statements of comprehensive loss, shareholders' equity and cash flows for each of the three years in the period ended December 31, 2019 and the related notes and our report dated February 25, 2020 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Iselin, New Jersey
February 25, 2020

INSMED INCORPORATED
Consolidated Balance Sheets
(in thousands, except par value and share data)

	As of December 31, 2019	As of December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 487,429	$ 495,072
Accounts receivable	19,232	5,515
Inventory	28,313	7,032
Prepaid expenses and other current assets	20,220	11,327
Total current assets	555,194	518,946
Intangibles, net	53,682	58,675
Fixed assets, net	60,180	22,636
Finance lease right-of-use assets	15,256	—
Operating lease right-of-use assets	37,673	—
Other assets	20,314	4,299
Total assets	$ 742,299	$ 604,556
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 13,184	$ 17,741
Accrued expenses	40,375	38,254
Accrued compensation	19,140	22,208
Finance lease liabilities	1,221	—
Operating lease liabilities	11,040	—
Other current liabilities	280	1,529
Total current liabilities	85,240	79,732
Debt, long-term	335,940	316,558
Finance lease liabilities, long-term	19,529	—
Operating lease liabilities, long-term	29,308	—
Other long-term liabilities	10,608	—
Total liabilities	480,625	396,290
Shareholders' equity:		
Common stock, $0.01 par value; 500,000,000 authorized shares, 89,682,387 and 77,307,521 issued and outstanding shares at December 31, 2019 and December 31, 2018, respectively	897	773
Additional paid-in capital	1,797,286	1,489,664
Accumulated deficit	(1,536,499)	(1,282,162)
Accumulated other comprehensive loss	(10)	(9)
Total shareholders' equity	261,674	208,266
Total liabilities and shareholders' equity	$ 742,299	$ 604,556

See accompanying notes to consolidated financial statements

INSMED INCORPORATED
Consolidated Statements of Comprehensive Loss
(in thousands, except per share data)

	Years Ended December 31,		
	2019	**2018**	**2017**
Revenues, net	$ 136,467	$ 9,835	$ —
Cost of product revenues (excluding amortization of intangible assets)	24,212	2,423	—
Gross profit	112,255	7,412	—
Operating expenses:			
Research and development	131,711	145,283	109,749
Selling, general and administrative	210,796	168,218	79,171
Amortization of intangible assets	4,993	1,249	—
Total operating expenses	347,500	314,750	188,920
Operating loss	(235,245)	(307,338)	(188,920)
Investment income	9,921	10,341	1,624
Interest expense	(27,705)	(25,472)	(5,925)
Loss on extinguishment of debt	—	(2,209)	—
Other (expense) income, net	(531)	602	300
Loss before income taxes	(253,560)	(324,076)	(192,921)
Provision (benefit) for income taxes	777	201	(272)
Net loss	$ (254,337)	$ (324,277)	$ (192,649)
Basic and diluted net loss per share	$ (3.01)	$ (4.22)	$ (2.89)
Weighted average basic and diluted common shares outstanding	84,560	76,889	66,576
Net loss	$ (254,337)	$ (324,277)	$ (192,649)
Other comprehensive income (loss):			
Foreign currency translation (losses) gains	(1)	(6)	62
Total comprehensive loss	$ (254,338)	$ (324,283)	$ (192,587)

See accompanying notes to audited consolidated financial statements

INSMED INCORPORATED
Consolidated Statements of Shareholders' Equity
(in thousands)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Loss	Total
	Shares	**Amount**				
Balance at January 1, 2017	62,020	$ 620	$ 919,164	$ (765,236)	$ (65)	$ 154,483
Comprehensive loss:						
Net loss				(192,649)		(192,649)
Other comprehensive income					62	62
Exercise of stock options	379	4	3,429			3,433
Net proceeds from issuance of common stock	14,123	141	377,515			377,656
Issuance of common stock for vesting of RSUs	89	1				1
Stock compensation expense			18,073			18,073
Balance at December 31, 2017	76,611	$ 766	$ 1,318,181	$ (957,885)	$ (3)	$ 361,059
Comprehensive loss:						
Net loss				(324,277)		(324,277)
Other comprehensive loss					(6)	(6)
Exercise of stock options and ESPP shares	645	6	8,809			8,815
Equity component of convertible debt			136,434			136,434
Issuance of common stock for vesting of RSUs	52	1				1
Stock compensation expense			26,240			26,240
Balance at December 31, 2018	77,308	$ 773	$ 1,489,664	$ (1,282,162)	$ (9)	$ 208,266
Comprehensive loss:						
Net loss				(254,337)		(254,337)
Other comprehensive loss					(1)	(1)
Exercise of stock options and ESPP shares	1,632	16	19,684			19,700
Net proceeds from issuance of common stock	10,658	107	260,967			261,074
Issuance of common stock for vesting of RSUs	84	1				1
Stock compensation expense			26,971			26,971
Balance at December 31, 2019	89,682	$ 897	$ 1,797,286	$ (1,536,499)	$ (10)	$ 261,674

See accompanying notes to audited consolidated financial statements

(in thousands)

	Years Ended December 31,		
	2019	2018	2017
Operating activities			
Net loss	$(254,337)	$(324,277)	$(192,649)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	5,188	3,577	2,901
Amortization of intangible assets	4,993	1,249	—
Stock-based compensation expense	26,971	26,240	18,073
Loss on extinguishment of debt	—	2,209	—
Amortization of debt issuance costs	1,397	1,350	118
Accretion of debt discount and back-end fee on debt	17,985	15,939	658
Finance lease amortization expense	360	—	—
Noncash operating lease expense	9,763	—	—
Changes in operating assets and liabilities:			
Accounts receivable	(13,717)	(5,515)	—
Inventory	(21,281)	(7,032)	—
Prepaid expenses and other current assets	(8,718)	(5,514)	(2,783)
Other assets	(16,008)	—	—
Accounts payable	(4,966)	3,870	3,604
Accrued expenses and other	4,789	19,916	5,201
Accrued compensation	(3,068)	10,011	5,260
Net cash used in operating activities	(250,649)	(257,977)	(159,617)
Investing activities			
Purchase of fixed assets	(42,268)	(13,090)	(3,001)
PARI milestone upon FDA approval	—	(1,724)	—
Net cash used in investing activities	(42,268)	(14,814)	(3,001)
Financing activities			
Proceeds from issuance of 1.75% convertible senior notes due 2025	—	450,000	—
Payment on extinguishment of debt	—	(2,835)	—
Payment of debt	—	(55,000)	—
Proceeds from issuance of common stock, net	261,074	—	377,656
Proceeds from exercise of stock options, ESPP, and RSU vesting	19,701	8,815	3,433
Payment of debt issuance costs	—	(14,237)	—
Proceeds from tenant improvement allowance	4,503	—	—
Net cash provided by financing activities	285,278	386,743	381,089
Effect of exchange rates on cash and cash equivalents	(4)	(45)	103
Net (decrease) increase in cash and cash equivalents	(7,643)	113,907	218,574
Cash and cash equivalents at beginning of period	495,072	381,165	162,591
Cash and cash equivalents at end of period	$ 487,429	$ 495,072	$ 381,165
Supplemental disclosures of cash flow information:			
Cash paid for interest	$ 7,883	$ 6,289	$ 5,165
Cash paid for income taxes	$ 339	$ 154	$ 166

See accompanying notes to audited consolidated financial statements

1. Description of Business and Basis of Presentation

Description of Business—Insmed is a global biopharmaceutical company on a mission to transform the lives of patients with serious and rare diseases. The Company's first commercial product, ARIKAYCE (amikacin liposome inhalation suspension), received accelerated approval in the United States (US) in September 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. Nontuberculous mycobacterial (NTM) lung disease caused by MAC (which the Company refers to as MAC lung disease) is a rare and often chronic infection that can cause irreversible lung damage and can be fatal. The Company's 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 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 Company was incorporated in the Commonwealth of Virginia on November 29, 1999 and its principal executive offices are located in Bridgewater, New Jersey. The Company has legal entities in the US, France, Germany, Ireland, Italy, the Netherlands, the United Kingdom (UK), Switzerland, Japan, and Bermuda.

The Company had $487.4 million in cash and cash equivalents as of December 31, 2019 and reported a net loss of $254.3 million for the year ended December 31, 2019. Historically, the Company has funded its operations primarily through public offerings of equity securities and debt financings. The Company commenced commercial shipments of ARIKAYCE in October 2018. The Company expects to continue to incur operating losses both at its US and certain international entities while funding research and development (R&D) activities for ARIKAYCE and its other pipeline programs, continuing commercialization activities for ARIKAYCE in the US, continuing to invest in pre-commercial and regulatory activities for ARIKAYCE in Europe and Japan, and funding other general and administrative activities.

The Company expects its future cash requirements to be substantial, and the Company may need to raise additional capital to fund operations, including the commercialization of ARIKAYCE and additional clinical trials related to ARIKAYCE, to develop INS1007 and INS1009 and to develop, acquire, in-license or co-promote other products or product candidates, including those that address orphan or rare diseases. The source, timing and availability of any future financing or other transaction will depend principally upon continued progress in the Company’s commercial, regulatory and development activities. Any equity or debt financing will also be contingent upon equity and debt market conditions and interest rates at the time. If the Company is unable to obtain sufficient additional funds when required, the Company may be forced to delay, restrict or eliminate all or a portion of its development programs, commercialization or business development efforts. The Company believes it currently has sufficient funds to meet its financial needs for at least the next 12 months.

Basis of Presentation—The consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries, Celtrix Pharmaceuticals, Inc., Insmed Holdings Limited, Insmed Ireland Limited, Insmed France SAS, Insmed Germany GmbH, Insmed Limited, Insmed Netherlands B.V., Insmed Bermuda Limited, Insmed Godo Kaisha, Insmed Switzerland GmbH, and Insmed Italy S.R.L.. All intercompany transactions and balances have been eliminated in consolidation.

2. Summary of Significant Accounting Policies

Use of Estimates—The preparation of the consolidated financial statements in conformity with accounting principles generally accepted in the United States (GAAP) requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. The Company bases its estimates and judgments on historical experience and on various other assumptions. The amounts of assets and liabilities reported in the Company's balance sheets and the amounts of revenues and expenses reported for each period presented are affected by estimates and assumptions, which are used for, but not limited to, the accounting for revenue allowances, stock-based compensation, income taxes, loss contingencies, and accounting for research and development costs. Actual results could differ from those estimates.

Investment Income and Interest Expense—Investment income consists of interest income earned on the Company's cash and cash equivalents. Interest expense consists primarily of interest costs related to the Company's debt.

Cash and Cash Equivalents—The Company considers cash equivalents to be highly liquid investments with maturities of three months or less from the date of purchase.

2. Summary of Significant Accounting Policies (Continued)

Fixed Assets, Net—Fixed assets are recorded at cost and are depreciated on a straight-line basis over the estimated useful lives of the assets. Estimated useful lives of three years to five years are used for computer equipment. Estimated useful lives of seven years are used for laboratory equipment, office equipment, manufacturing equipment and furniture and fixtures. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset. Long-lived assets are reviewed for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to estimated undiscounted future cash flows expected to be generated by the asset. If the carrying amount of an asset exceeds its estimated future cash flows, then an impairment charge is recognized for the amount by which the carrying value of the asset exceeds the fair value of the asset.

Intangible Assets, Net—Finite-lived intangible assets are measured at their respective fair values on the date they were recorded and, with respect to the acquired ARIKAYCE R&D intangible asset, at the date of subsequent adjustments of fair value. The fair values assigned to the Company's intangible assets are based on reasonable estimates and assumptions given available facts and circumstances.

Impairment Assessment—The Company reviews the recoverability of its finite-lived intangible assets and long-lived assets for indicators of impairments. Events or circumstances that may require an impairment assessment include negative clinical trial results, a significant decrease in the market price of the asset, or a significant adverse change in legal factors or the manner in which the asset is used. If such indicators are present, the Company assess the recoverability of affected assets by determining if the carrying value of such assets is less than the sum of the undiscounted future cash flows of the assets. If such assets are found to not be recoverable, the Company measures the amount of the impairment by comparing to the carrying value of the assets to the fair value of the assets. The Company determined that no indicators of impairment of finite-lived intangible assets or long-lived assets existed at December 31, 2019.

Debt Issuance Costs—Debt issuance costs are amortized to interest expense using the effective interest rate method over the term of the debt. Debt issuance costs paid to the lender and third parties are reflected as a discount to the debt in the consolidated balance sheets. Unamortized debt issuance costs associated with extinguished debt are expensed in the period of the extinguishment.

Fair Value Measurements—The Company categorizes its financial assets and liabilities measured and reported at fair value in the financial statements on a recurring basis based upon the level of judgment associated with the inputs used to measure their fair value. Hierarchical levels, which are directly related to the amount of subjectivity associated with the inputs used to determine the fair value of financial assets and liabilities, are as follows:

- Level 1 — Inputs are unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date.
- Level 2 — Inputs (other than quoted prices included in Level 1) are either directly or indirectly observable for the assets or liability through correlation with market data at the measurement date and for the duration of the instrument’s anticipated life.
- Level 3 — Inputs reflect management’s best estimate of what market participants would use in pricing the asset or liability at the measurement date. Consideration is given to the risk inherent in the valuation technique and the risk inherent in the inputs to the model.

Each major category of financial assets and liabilities measured at fair value on a recurring basis is categorized based upon the lowest level of significant input to the valuations. The fair value hierarchy also requires an entity to maximize the use of observable inputs and minimize the use of unobservable inputs when measuring fair value. Financial instruments in Level 1 generally include US treasuries and mutual funds listed in active markets.

The Company's only financial assets and liabilities which were measured at fair value as of December 31, 2019 and December 31, 2018 were Level 1 assets comprised of cash and cash equivalents. The Company's cash and cash equivalents permit daily redemption and the fair values of these investments are based upon the quoted prices in active markets provided by the holding financial institutions. The following table shows assets and liabilities that are measured at fair value on a recurring basis and their carrying value (in millions):

2. Summary of Significant Accounting Policies (Continued)

	As of December 31, 2019			
		Fair Value		
	Carrying Value	Level 1	Level 2	Level 3
Cash and cash equivalents	$ 487.4	$ 487.4	$ —	$ —

	As of December 31, 2018			
		Fair Value		
	Carrying Value	Level 1	Level 2	Level 3
Cash and cash equivalents	$ 495.1	$ 495.1	$ —	$ —

The Company recognizes transfers between levels within the fair value hierarchy, if any, at the end of each quarter. There were no transfers in or out of Level 1, Level 2 or Level 3 during 2019 and 2018.

As of December 31, 2019 and 2018, the Company held no securities that were in an unrealized loss or gain position.

The Company reviews the status of each security quarterly to determine whether an other-than-temporary impairment has occurred. In making its determination, the Company considers a number of factors, including: (1) the significance of the decline; (2) whether the security was rated below investment grade; (3) how long the security has been in an unrealized loss position; and (4) the Company's ability and intent to retain the investment for a sufficient period of time for it to recover.

The estimated fair value of the liability component of the 1.75% convertible senior notes due 2025 (the Convertible Notes) (categorized as a Level 2 liability for fair value measurement purposes) as of December 31, 2019 was $435.4 million, determined using current market factors and the ability of the Company to obtain debt on comparable terms to the Convertible Notes. The $335.9 million carrying value of the Convertible Notes as of December 31, 2019 excludes the $107.0 million of the unamortized portion of the debt discount.

Foreign Currency—The Company has operations in the US, France, Germany, Ireland, Italy, the Netherlands, Switzerland, the United Kingdom (UK), and Japan. The results of its non-US dollar based functional currency operations are translated to US dollars at the average exchange rates during the period. Assets and liabilities are translated at the exchange rate prevailing at the balance sheet date. Equity is translated at the prevailing exchange rate at the date of the equity transaction. Translation adjustments are included in shareholders' equity, as a component of accumulated other comprehensive loss.

The Company realizes foreign currency transaction gains (losses) in the normal course of business based on movements in the applicable exchange rates. These gains (losses) are included as a component of other income, net.

Concentration of Credit Risk—Financial instruments that potentially subject the Company to concentrations of credit risk consist primarily of cash and cash equivalents. The Company places its cash equivalents with high credit-quality financial institutions and may invest its short-term investments in US treasury securities, mutual funds and government agency bonds. The Company has established guidelines relative to credit ratings and maturities that seek to maintain safety and liquidity.

The Company is exposed to risks associated with extending credit to customers related to the sale of products. The Company does not require collateral to secure amounts due from its customers. The following table presents the percentage of gross product revenue represented by the Company's three largest customers as of the year ended December 31, 2019.

	Percentage of Total Gross Product Revenue	
	2019	2018
Customer A	31%	27 %
Customer B	26%	37 %
Customer C	22%	15 %

2. Summary of Significant Accounting Policies (Continued)

The Company did not have product revenue prior to US FDA approval of ARIKAYCE in September 2018. The Company relies on third-party manufacturers and suppliers for manufacturing and supply of its products. The inability of the suppliers or manufacturers to fulfill supply requirements of the Company could materially impact future operating results. A change in the relationship with the suppliers or manufacturer, or an adverse change in their business, could materially impact future operating results.

Revenue Recognition—In accordance with Accounting Standards Codification (ASC) 606, Revenue from Contracts with Customers, the Company recognizes revenue when a customer obtains control of promised goods or services, in an amount that reflects the consideration the Company expects to receive in exchange for the goods or services provided. To determine revenue recognition for arrangements within the scope of ASC 606, the Company performs the following five steps: (1) identify the contracts with a customer; (2) identify the performance obligations in the contract; (3) determine the transaction price; (4) allocate the transaction price to the performance obligations in the contract; and (5) recognize revenue when or as the entity satisfies a performance obligation. At contract inception, the Company assesses the goods or services promised within each contract and determines those that are performance obligations and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when or as the performance obligation is satisfied. For all contracts that fall into the scope of ASC 606, the Company has identified one performance obligation: the sale of ARIKAYCE to its customers. The Company has not incurred or capitalized any incremental costs associated with obtaining contracts with customers.

Product revenues consist primarily of sales of ARIKAYCE in the US. Product revenues are recognized once the Company performs and satisfies all five steps mentioned above. In October 2018, the Company began shipping ARIKAYCE to its customers in the US, which include specialty pharmacies and specialty distributors.

Revenue is recorded at net selling price (transaction price), which includes estimates of variable consideration for which reserves are established for (a) customer credits, such as invoice discounts for prompt pay and specialty pharmacies fees, (b) estimated government rebates, such as Medicaid and Medicare Part D reimbursements, and estimated managed care rebates, (c) estimated chargebacks, and (d) estimated costs of co-payment assistance. These reserves are based on the amounts earned or to be claimed on the related sales and are classified as reductions of accounts receivable (prompt pay discounts and chargebacks), prepaid expenses (co-payment assistance), or as a current liability (rebates). Where appropriate, these estimates take into consideration a range of possible outcomes which are probability-weighted for relevant factors such as the Company's historical experience, current contractual and statutory requirements, and forecasted customer buying and payment patterns. Overall, these reserves reflect the Company's best estimates of the amount of consideration to which it is entitled based on the terms of the applicable contract. The amount of variable consideration included in the transaction price may be constrained and is included in the net sales price only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from the Company's estimates. If actual results in the future vary from estimates, the Company adjusts these estimates, which would affect net product revenue and earnings in the period such variances become known.

Customer credits: The Company's customers are offered various forms of consideration, including fees for enhanced services and prompt payment discounts. The payment terms for sales to specialty pharmacies for prompt payment discounts and fees for services are based on contractual rates agreed with the respective specialty pharmacies. The Company anticipates that its customers will earn these discounts and fees and, therefore, deduct the full amount of these discounts and fees from total gross product revenues at the time such revenues are recognized.

Rebates: The Company contracts with government agencies and managed care organizations or collectively, third-party payors, so that ARIKAYCE will be eligible for purchase by, or partial or full reimbursement from, such third-party payors. The Company estimates the rebates it will provide to third-party payors and deducts these estimated amounts from total gross product revenues at the time the revenues are recognized. These reserves are recorded in the same period in which the revenue is recognized, resulting in a reduction of product revenue and the establishment of a current liability. The current liability is included in accrued expenses on the consolidated balance sheets. The Company estimates the rebates that it will provide to third-party payors based upon (i) the Company’s contracts with these third-party payors, (ii) the government mandated discounts applicable to government-funded programs, (iii) a range of possible outcomes that are probability-weighted for the estimated payer mix, and (iv) information obtained from the Company’s specialty pharmacies.

2. Summary of Significant Accounting Policies (Continued)

Chargebacks: Chargebacks are discounts that occur when certain contracted customers, currently public health service institutions and federal government entities purchasing via the Federal Supply Schedule, purchase directly from the Company's specialty distributor. Contracted customers generally purchase the product at a discounted price and the specialty distributor, in turn, charges back to the Company the difference between the price they initially paid and the discounted price paid by the contracted customers. The Company estimates chargebacks provided to the specialty distributor and deducts these estimated amounts from gross product revenues, and from accounts receivable, at the time revenues are recognized.

Co-payment assistance: Patients who have commercial insurance and meet certain eligibility requirements may receive co-payment assistance. Based upon the terms of the program and information regarding programs provided for similar specialty pharmaceutical products, the Company estimates the average co-pay mitigation amounts and the percentage of patients that it expects to participate in the program in order to establish accruals for co-payment assistance. These reserves are recorded in the same period in which the related revenue is recognized, resulting in a reduction of product revenue. The Company adjusts its accruals for co-pay assistance based on actual redemption activity and estimates of future redemptions related to sales in the current period.

If any, or all, of the Company's actual experience vary from the estimates above, the Company may need to adjust prior period accruals, affecting revenue in the period of adjustment.

The following table provides a summary roll-forward of the Company's sales allowances and related accruals for the years ended December 31, 2019 and 2018, which have been deducted in arriving at revenues, net (in thousands).

	Customer Credits, Fees and Discounts	Rebates, Chargebacks and Co-pay Assistance	Total
Balance as of January 1, 2019	$ 234	$ 688	$ 922
Allowances for current period sales	3,151	12,059	15,210
Allowances for prior period sales	14	26	40
Payments and credits	(2,935)	(7,602)	(10,537)
Balance as of December 31, 2019	$ 464	$ 5,171	$ 5,635
Balance as of January 1, 2018	$ —	$ —	$ —
Allowances for current period sales	335	849	1,184
Payments and credits	(101)	(161)	(262)
Balance as of December 31, 2018	$ 234	$ 688	$ 922

The Company also recognizes revenue related to early access programs (EAPs) in Europe, consisting of sales to the French National Agency for Medicines and Health Products Safety, which granted ARIKAYCE a Temporary Authorization for Use (Autorisation Temporaire d'Utilisation or ATU) and from the named patient program in Germany, both compassionate use programs. EAPs are intended to make products available on a named patient basis before they are commercially available in accordance with local regulations.

Inventory and Cost of Product Revenues (excluding amortization of intangible assets)—Inventory is stated at the lower of cost and net realizable value. The Company began capitalizing inventory costs following FDA approval of ARIKAYCE in September 2018. Inventory is sold on a first-in, first-out (FIFO) basis. The Company periodically reviews inventory for expiry and obsolescence and, if necessary, writes down accordingly. If quality specifications are not met during the manufacturing process, such inventory is written off to cost of product revenues (excluding amortization of intangible assets) in the period identified.

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, and

2. Summary of Significant Accounting Policies (Continued)

allocation of overhead costs, in addition to royalty expenses and revenue-based milestones. Cost is determined using a standard cost method, which approximates actual cost, and assumes a first-in, first-out (FIFO) flow of goods.

Prior to FDA approval of ARIKAYCE, the Company expensed all inventory related costs in the period incurred. Inventory used for clinical development purposes is expensed to research and development (R&D) expense when consumed.

Research and Development—R&D expenses consist primarily of salaries, benefits and other related costs, including stock-based compensation, for personnel serving in the Company's research and development functions, including medical affairs. R&D expense also includes other internal operating expenses, the cost of manufacturing a product candidate, including the medical devices for drug delivery, for clinical study, the cost of conducting clinical studies, and the cost of conducting preclinical and research activities. In addition, R&D expenses include payments to third parties for the license rights to products in development (prior to marketing approval), such as INS1007. The Company's expenses related to manufacturing its product candidates and medical devices for clinical study are primarily related to activities at contract manufacturing organizations that manufacture INS1007 and INS1009. The Company's expenses related to clinical trials are primarily related to activities at contract research organizations that conduct and manage clinical trials on the Company's behalf. These contracts set forth the scope of work to be completed at a fixed fee or amount per patient enrolled. Payments under these contracts primarily depend on performance criteria such as the successful enrollment of patients or the completion of clinical trial milestones as well as time-based fees. Expenses are accrued based on contracted amounts applied to the level of patient enrollment and to activity according to the clinical trial protocol. Nonrefundable advance payments for goods or services that will be used or rendered for future research and development activities are deferred and capitalized. Such amounts are then recognized as an expense as the related goods are delivered or the services are performed, or when the goods or services are no longer expected to be provided.

Stock-based Compensation—The Company recognizes stock-based compensation expense for awards of equity instruments to employees and directors based on the grant-date fair value of those awards. The grant-date fair value of the award is recognized as compensation expense ratably over the requisite service period, which generally equals the vesting period of the award, and if applicable, is adjusted for expected forfeitures. The Company may also grant performance-based stock options to employees from time-to-time. The grant-date fair value of performance-based stock options is recognized as compensation expense over the implicit service period using the accelerated attribution method once it is probable that the performance condition will be achieved. Stock-based compensation expense is included in both R&D and SG&A expenses in the consolidated statements of comprehensive loss.

Income Taxes—The Company accounts for income taxes under the asset and liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and operating loss carry forwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period that includes the enactment date.

A valuation allowance is recorded to reduce the deferred tax assets to the amount that is expected to be realized. In evaluating the need for a valuation allowance, the Company takes into account various factors, including the expected level of future taxable income and available tax planning strategies. If actual results differ from the assumptions made in the evaluation of a valuation allowance, the Company records a change in valuation allowance through income tax expense in the period such determination is made.

The Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained on examination by taxing authorities, based solely on the technical merits of the position. The tax benefits recognized in the financial statements from such a position should be measured based on the largest benefit that has a greater than 50% likelihood to be sustained upon ultimate settlement. As any adjustment to the Company’s uncertain tax positions would not result in a cash tax liability, it has not recorded any accrued interest or penalties related to its uncertain tax positions.

The Company's policy for interest and penalties related to income tax exposures is to recognize interest and penalties as a component of the income tax provision (benefit) in the consolidated statements of comprehensive loss.

Net Loss Per Share—Basic net loss per share is computed by dividing net loss attributable to common shareholders by the weighted average number of common shares outstanding during the period. Diluted net loss per share is computed by dividing net loss by the weighted average number of common shares and other dilutive securities outstanding during the period.

2. Summary of Significant Accounting Policies (Continued)

Potentially dilutive securities from stock options and restricted stock units would be anti-dilutive as the Company incurred a net loss in all periods presented. Potentially dilutive common shares resulting from the assumed exercise of outstanding stock options would be determined based on the treasury stock method.

The following table sets forth the reconciliation of the weighted average number of shares used to compute basic and diluted net loss per share for the years ended December 31, 2019, 2018 and 2017.

	Years Ended December 31,		
	2019	2018	2017
	(in thousands, except per share amounts)		
Numerator:			
Net loss	$ (254,337)	$ (324,277)	$ (192,649)
Denominator:			
Weighted average common shares used in calculation of basic net loss per share:	84,560	76,889	66,576
Effect of dilutive securities:			
Common stock options	—	—	—
Unvested restricted stock and restricted stock units	—	—	—
Convertible debt securities	—	—	—
Weighted average common shares outstanding used in calculation of diluted net loss per share	84,560	76,889	66,576
Net loss per share:			
Basic and diluted	$ (3.01)	$ (4.22)	$ (2.89)

The following potentially dilutive securities have been excluded from the computations of diluted weighted average common shares outstanding as of December 31, 2019, 2018 and 2017 as their effect would have been anti-dilutive (in thousands).

	As of December 31,		
	2019	2018	2017
Common stock options	10,493	9,382	8,609
Unvested restricted stock and restricted stock units	501	228	47
Convertible debt securities	11,492	11,492	—

Leases—In February 2016, the FASB issued ASU 2016-02, Leases (Topic 842) in order to increase transparency and comparability among organizations by recognizing lease assets and lease liabilities on the balance sheet for those leases classified as operating leases under previous generally accepted accounting principles. ASU 2016-02 requires a lessee to recognize a liability to make lease payments (the lease liability) and a right-of-use (ROU) asset representing its right to use the underlying asset for the lease term on the balance sheet.

A lease is a contract, or part of a contract, that conveys the right to control the use of explicitly or implicitly identified property, plant or equipment in exchange for consideration. Control of an asset is conveyed to the Company if the Company obtains the right to obtain substantially all of the economic benefits of the asset or the right to direct the use of the asset. The Company recognizes ROU assets and lease liabilities at the lease commencement date based on the present value of future, fixed lease payments over the term of the arrangement. ROU assets are amortized on a straight-line basis over the term of the lease. Lease liabilities accrete to yield and are reduced at the time when the lease payment is payable to the vendor. Variable lease payments are recognized at the time when the event giving rise to the payment occurs and are recognized in the statement of comprehensive loss in the same line item as expenses arising from fixed lease payments.

In accordance with Topic 842, leases are measured at present value using the rate implicit in the lease or, if the implicit rate is not determinable, the lessee's implicit borrowing rate. As the implicit rate is not typically available, the Company uses its

2. Summary of Significant Accounting Policies (Continued)

implicit borrowing rate based on the information available at the lease commencement date to determine the present value of future lease payments. The implicit borrowing rate approximates the rate the Company would pay to borrow on a collateralized basis over a similar term an amount equal to the lease payments.

Financial information presented prior to January 1, 2019 has not been adjusted and is presented in accordance with ASC 840. Refer to the Recently Adopted Accounting Pronouncements section within this note below and Note 7 - Leases for details about the Company's lease portfolio, including Topic 842 required disclosures.

Segment Information—The Company currently operates in one business segment, which is the development and commercialization of therapies for patients with rare diseases. A single management team that reports to the Chief Executive Officer comprehensively manages the entire business. The Company does not operate separate lines of business with respect to its products or product candidates. Accordingly, the Company has one reportable segment.

Recently Adopted Accounting Pronouncements—Topic 842 was effective for fiscal years beginning after December 15, 2018 (including interim periods within those years) and early adoption was permitted. In August 2018, the FASB issued ASU 2018-11, Targeted Improvements to ASC 842, which provided a transition option in which an entity would initially apply ASU 2016-02 at the adoption date and recognize a cumulative-effect adjustment to the opening balance of retained earnings in the period of adoption. The Company used the new transition option and the package of practical expedients that allowed it to not reassess: (1) whether any expired or existing contracts are or contain leases; (2) lease classification for any expired or existing leases; and (3) initial direct costs for any expired or existing leases. The Company also used the practical expedient that allows it to treat the lease and non-lease components of its leases as a single component. The Company adopted ASU 2016-02 effective January 1, 2019. The impact of the adoption of ASU 2016-02 on the consolidated balance sheet was $47.4 million.

In August 2016, the Financial Accounting Standards Board (FASB) issued Accounting Standard Update (ASU) 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments*, which addressed eight specific cash flow issues with the objective of reducing the existing diversity in practice. Among the updates, the standard requires debt extinguishment costs to be classified as cash outflows for financing activities. This standard update became effective as of the first quarter of 2018. As a result of the adoption of the standard, in the first quarter of 2018, the Company reported a $2.2 million loss on extinguishment of debt in the operating activities section of its consolidated statement of cash flows. The Company had no material debt extinguishment costs prior to the first quarter of 2018. The impact of adopting this standard was not material to the Company.

Recent Accounting Pronouncements (Not Yet Adopted)—In June 2016, the FASB issued ASU 2016-13, Financial Instruments - Credit Losses which requires financial assets measured at an amortized cost basis to be presented at the net amount expected to be collected. The measurement of expected credit losses is based on relevant information about past events, including historical experience, current conditions, and reasonable and supportable forecasts that affect the collectability of the reported amount. ASU 2016-13 is effective for fiscal years beginning after December 15, 2019 and the Company will adopt the standard effective January 1, 2020. Different aspects of the guidance require modified retrospective or prospective adoption. The Company has performed an assessment and has determined that adoption will not have a material impact on its consolidated financial statements.

3. Inventory

The Company's inventory balance consists of the following (in thousands):

	As of December 31,	
	2019	2018
Raw materials	$ 16,048	$ 2,145
Work-in-process	6,420	4,567
Finished goods	5,845	320
	$ 28,313	$ 7,032

Inventory is stated at the lower of cost and net realizable value and consists of raw materials, work-in-process and finished goods. The Company began capitalizing inventory costs following FDA approval of ARIKAYCE in September 2018. The Company has not recorded any significant inventory write downs since that time. The Company currently uses a limited number of third-party contract manufacturing organizations (CMOs) to produce its inventory.

4. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	As of December 31,	
	2019	2018
Accrued clinical trial expenses	$ 5,598	$ 6,635
Accrued professional fees	12,581	13,398
Accrued technical operation expenses	6,446	9,371
Accrued royalty payable	3,117	409
Accrued interest payable	3,631	3,631
Accrued sales allowances and related costs	5,267	818
Accrued construction costs	2,689	2,946
Other accrued expenses	1,046	1,046
	$ 40,375	$ 38,254

5. Intangible Assets, Net

As of December 31, 2019, the Company's finite-lived intangible assets consisted of acquired ARIKAYCE R&D, which resulted from the initial amount recorded at the time of the Company's merger with Transave in 2010 and subsequent adjustments in the value, and a milestone paid to PARI of $1.7 million for the license to use PARI's Lamira® Nebulizer System for the delivery of ARIKAYCE to patients as a result of the FDA approval of ARIKAYCE in September 2018 (the PARI milestone). Total intangible assets, net was $53.7 million and $58.7 million as of December 31, 2019 and 2018, respectively.

The Company began amortizing its finite-lived intangible assets in October 2018, over ARIKAYCE's initial regulatory exclusivity period of 12 years. Amortization of these assets during each of the next five years is estimated to be approximately $5.0 million per year.

A rollforward of the Company's finite-lived intangible assets for the years ended December 31, 2019 and 2018 follows (in thousands):

	2019			
Intangible Asset	January 1,	Additions	Amortization	December 31,
Acquired ARIKAYCE R&D	$ 56,988	$ —	$ (4,849)	$ 52,139
PARI milestone	1,687	—	(144)	1,543
	$ 58,675	$ —	$ (4,993)	$ 53,682

	2018			
Intangible Asset	January 1,	Additions	Amortization	December 31,
Acquired ARIKAYCE R&D	$ 58,200	$ —	$ (1,212)	$ 56,988
PARI milestone	—	1,724	(37)	1,687
	$ 58,200	$ 1,724	$ (1,249)	$ 58,675

6. Fixed Assets, Net

Fixed assets are stated at cost and depreciated using the straight-line method, based on useful lives as follows (in thousands):

Asset Description	Estimated Useful Life (years)	As of December 31, 2019	As of December 31, 2018
Lab equipment	7	$ 9,634	$ 7,935
Furniture and fixtures	7	5,908	2,320
Computer hardware and software	3 - 5	6,806	3,796
Office equipment	7	154	65
Manufacturing equipment	7	1,567	1,166
Leasehold improvements	lease term	33,852	7,202
Construction in progress (CIP)	—	21,526	14,325
		79,447	36,809
Less accumulated depreciation		(19,267)	(14,173)
Fixed assets, net		$ 60,180	$ 22,636

Fixed assets, net of depreciation, increased to $60.2 million during the year ended December 31, 2019 from $22.6 million in 2018. The $37.5 million increase was primarily due to the $26.7 million and $7.2 million increases in leasehold improvements and construction in progress, respectively, related to the Company's new corporate headquarters and the long-term capacity increase of the Patheon manufacturing facility.

Depreciation expense was $5.2 million, $3.6 million and $2.9 million for the years ended December 31, 2019, 2018 and 2017, respectively.

7. Leases

In February 2016, the FASB issued ASU 2016-02, Leases (Topic 842) in order to increase transparency and comparability among organizations by recognizing lease assets and lease liabilities on the balance sheet. ASU 2016-02 requires a lessee to recognize a liability to make lease payments (the lease liability) and a right-of-use (ROU) asset representing its right to use the underlying asset for the lease term on the balance sheet.

A lease is a contract, or part of a contract, that conveys the right to control the use of explicitly or implicitly identified property, plant or equipment in exchange for consideration. Control of an asset is conveyed to the Company if the Company obtains the right to obtain substantially all of the economic benefits of the asset or the right to direct the use of the asset. The Company recognizes ROU assets and lease liabilities at the lease commencement date based on the present value of future, fixed lease payments over the term of the arrangement. ROU assets are amortized on a straight-line basis over the term of the lease. Lease liabilities accrete to yield and are reduced at the time when the lease payment is payable to the vendor. Variable lease payments are recognized at the time when the event giving rise to the payment occurs and are recognized in the statement of comprehensive loss in the same line item as expenses arising from fixed lease payments.

In accordance with Topic 842, leases are measured at present value using the rate implicit in the lease or, if the implicit rate is not determinable, the lessee's implicit borrowing rate. As the implicit rate is not typically available, the Company uses its implicit borrowing rate based on the information available at the lease commencement date to determine the present value of future lease payments. The implicit borrowing rate approximates the rate the Company would pay to borrow on a collateralized basis over a similar term an amount equal to the lease payments.

In order to determine the appropriate discount rate for each lease, the Company determined its public credit rating and constructed debt yield curves. The debt yield curves were adjusted to reflect a collateral borrowing and differences in foreign currencies, where applicable, as well as to match the term of each lease.

7. Leases (Continued)

Financial information presented prior to January 1, 2019 has not been adjusted and is presented in accordance with ASC 840. Refer to the Recently Adopted Accounting Pronouncements section within Note 2 - Summary of Significant Accounting Policies note.

The Company's lease portfolio consists primarily of office space, manufacturing facilities and fleet vehicles. All of the Company's leases are classified as operating leases, except for the Company's corporate headquarters lease, which is classified as a finance lease. The terms of the Company's lease agreements that have commenced range from less than one year to ten years, ten months. In its assessment of the term of each such lease, the Company has not included any options to extend or terminate the lease due to the absence of economic incentives in its lease agreements. As permitted by the practical expedient in ASU 2016-02, leases that qualify for treatment as a short-term lease are expensed as incurred. These short-term leases are not material to the Company's financial position. Furthermore, the Company has elected the practical expedient to not separate lease and non-lease components for all classes of underlying assets. The Company's leases do not contain residual value guarantees and it does not sublease any of its leased assets.

The Company outsources its manufacturing operations to CMOs. Upon review of the agreements with its CMOs, the Company determined that these contracts contain embedded leases for dedicated manufacturing facilities. The Company obtains substantially all of the economic benefits from the use of the manufacturing facilities, has the right to direct how and for what purpose the facility is used throughout the period of use, and the supplier does not have the right to change the operating instructions of the facility. The operating lease right-of-use assets and corresponding lease liabilities associated with the manufacturing facilities is the sum of the minimum guarantees over the life of the production contracts.

In September 2018, the Company entered into the agreement to lease its new corporate headquarters in Bridgewater, NJ, consisting of 117,022 square feet. The lease term commenced in the fourth quarter of 2019 and is accounted for as a finance lease. The initial lease term expires in June 2030.

The table below summarizes the Company's total lease costs included in its consolidated financial statements, as well as other required quantitative disclosures (in thousands).

	As of December 31, 2019	
Finance lease cost:		
Amortization of right-of-use assets	$ 360	
Interest on lease liabilities	440	
Total finance lease cost		$ 800
Operating lease cost		12,218
Total lease cost		$ 13,018
Other information:		
Cash paid for amounts included in the measurement of lease liabilities		
Operating cash flows for finance leases		$ —
Operating cash flows for operating leases		$ 10,060
Financing cash flows for finance leases		$ (4,503)
Right-of-use assets obtained in exchange for new finance lease liabilities		$ 20,310
Right-of-use assets obtained in exchange for new operating lease liabilities		$ 47,436
Weighted average remaining lease term - finance leases		10.6 years
Weighted average remaining lease term - operating leases		5.0 years
Weighted average discount rate - finance leases		8.6 %
Weighted average discount rate - operating leases		7.4 %

The table below presents the maturity of lease liabilities on an annual basis for the remaining years of the Company's commenced lease agreements (in thousands).

7. Leases (Continued)

Year Ending December 31,	Finance Lease	Operating Leases
2020	$ 2,938	$ 13,415
2021	2,996	10,306
2022	2,280	6,000
2023	2,080	6,000
2024	3,172	6,000
Thereafter	18,784	6,000
Total	32,250	47,721
Less: present value discount	11,500	7,373
Present value of lease liabilities	$ 20,750	$ 40,348
Balance Sheet Classification at December 31, 2019:		
Current lease liabilities	$ 1,221	$ 11,040
Long-term lease liabilities	19,529	29,308
Total lease liabilities	$ 20,750	$ 40,348

In addition to the Company's lease agreements that have previously commenced and are reflected in the consolidated financial statements, the Company has entered into additional lease agreements that have not yet commenced. The Company entered into certain agreements with Patheon related to increasing its long-term production capacity for ARIKAYCE commercial inventory. The Company has determined that these agreements with Patheon contain an embedded lease for the manufacturing facility and the specialized equipment contained therein. Costs of $17.9 million incurred by the Company under these additional agreements have been classified within other assets in the Company's consolidated balance sheet. Upon the commencement date, prepaid costs and minimum guarantees specified in the agreement will be combined to establish an operating lease right-of-use asset and operating lease liability.

8. Debt

In January 2018, the Company completed an underwritten public offering of the Convertible Notes, in which the Company sold $450.0 million aggregate principal amount of Convertible Notes, including the exercise in full of the underwriters' option to purchase additional Convertible Notes of $50.0 million. The Company's net proceeds from the offering, after deducting underwriting discounts and commissions and other offering expenses of $14.2 million, were approximately $435.8 million. The Convertible Notes bear interest payable semiannually in arrears on January 15 and July 15 of each year, beginning on July 15, 2018. The Convertible Notes mature on January 15, 2025, unless earlier converted, redeemed, or repurchased.

On or after October 15, 2024, until the close of business on the second scheduled trading day immediately preceding January 15, 2025, holders may convert their Convertible Notes at any time. Upon conversion, holders may receive cash, shares of the Company's common stock or a combination of cash and shares of the Company's common stock, at the Company's option. The initial conversion rate is 25.5384 shares of common stock per $1,000 principal amount of Convertible Notes (equivalent to an initial conversion price of approximately $39.16 per share of common stock). The conversion rate will be subject to adjustment in some events but will not be adjusted for any accrued and unpaid interest.

Holders may convert their Convertible Notes prior to October 15, 2024, only under the following circumstances, subject to the conditions set forth in an indenture, dated as of January 26, 2018, between the Company and Wells Fargo Bank, National Association (Wells Fargo), as trustee, as supplemented by the first supplemental indenture, dated January 26, 2018, between the Company and Wells Fargo (as supplemented, the Indenture): (i) during the five business day period immediately after any five consecutive trading day period (the measurement period) in which the trading price per $1,000 principal amount of convertible notes, as determined following a request by a holder of the convertible notes, for each trading day of the measurement period was less than 98% of the product of the last reported sale price of the common stock and the conversion rate on such trading day, (ii) the Company elects to distribute to all or substantially all holders of the common stock (a) any

8. Debt (Continued)

rights, options or warrants (other than in connection with a stockholder rights plan for so long as the rights issued under such plan have not detached from the associated shares of common stock) entitling them, for a period of not more than 45 days from the declaration date for such distribution, to subscribe for or purchase shares of common stock at a price per share that is less than the average of the last reported sale prices of the common stock for the 10 consecutive trading day period ending on, and including, the trading day immediately preceding the declaration date for such distribution, or (b) the Company's assets, debt securities or rights to purchase securities of the Company, which distribution has a per share value, as reasonably determined by the board of directors, exceeding 10% of the last reported sale price of the common stock on the trading day immediately preceding the declaration date for such distribution, (iii) if a transaction or event that constitutes a fundamental change or a make-whole fundamental change occurs, or if the Company is a party to (a) a consolidation, merger, combination, statutory or binding share exchange or similar transaction, pursuant to which the common stock would be converted into, or exchanged for, cash, securities or other property or assets, or (b) any sale, conveyance, lease or other transfer or similar transaction in one transaction or a series of transactions of all or substantially all of the consolidated assets of the Company and its subsidiaries, taken as a whole, all or any portion of the Convertible Notes may be surrendered by a holder for conversion at any time from or after the date that is 30 scheduled trading days prior to the anticipated effective date of the transaction, (iv) if during any calendar quarter commencing after the calendar quarter ending on March 31, 2018 (and only during such calendar quarter), the last reported sale price of the common stock for at least 20 trading days (whether or not consecutive) during the period of 30 consecutive trading days ending on the last trading day of the immediately preceding calendar quarter is greater than or equal to 130% of the conversion price on each applicable trading day, or, (v) if the Company sends a notice of redemption, a holder may surrender all or any portion of its Convertible Notes, to which the notice of redemption relates, for conversion at any time on or after the date the applicable notice of redemption was sent until the close of business on (a) the second business day immediately preceding the related redemption date or (b) if the Company fails to pay the redemption price on the redemption date as specified in such notice of redemption, such later date on which the redemption price is paid.

The Convertible Notes can be settled in cash, common stock, or a combination of cash and common stock at the Company's option, and thus, the Company determined the embedded conversion options in the convertible notes are not required to be separately accounted for as a derivative. However, since the Convertible Notes are within the scope of the accounting guidance for cash convertible instruments, the Company is required to separate the Convertible Notes into liability and equity components. The carrying amount of the liability component was calculated by measuring the fair value of a similar liability that does not have an associated equity component. The fair value was based on data from readily available pricing sources which utilize market observable inputs and other characteristics for similar types of instruments. The carrying amount of the equity component representing the embedded conversion option was determined by deducting the fair value of the liability component from the gross proceeds of the Convertible Notes. The excess of the principal amount of the liability component over its carrying amount is amortized to interest expense over the expected life of a similar liability that does not have an associated equity component using the effective interest method. The equity component is not remeasured as long as it continues to meet the conditions for equity classification in the accounting guidance for contracts in an entity's own equity. The fair value of the liability component of the Convertible Notes on the date of issuance was estimated at $309.1 million using an effective interest rate of 7.6%, and accordingly, the residual equity component on the date of issuance was $140.9 million. The discount is being amortized to interest expense over the term of the Convertible Notes and has a remaining period of approximately 5.04 years.

For the twelve months ended December 31, 2019, total interest expense related to the Convertible Notes was $27.3 million, which includes the contractual interest coupon payable semi-annually in cash, the amortization of the issuance costs, and accretion of debt discount, as described in the table below. The following table presents the carrying value of the Company's debt balance as of December 31, 2019 (in thousands):

	As of December 31, 2019
1.75% convertible senior notes due 2025	$ 450,000
Debt issuance costs, unamortized	(7,043)
Discount on debt	(107,017)
Long-term debt, net	$ 335,940

As of December 31, 2019, future principal repayments of the debt for each of the fiscal years through maturity were as follows (in thousands):

8. Debt (Continued)

Year Ending December 31:	
2020	$ —
2021	—
2022	—
2023	—
2024 and thereafter	450,000
	$ 450,000

In February 2018, the Company used part of the net proceeds from the issuance of the Convertible Notes to pay off its outstanding debt to Hercules Capital (Hercules). The payments to Hercules consisted of $55.0 million for the principal amount and an additional $3.2 million in back-end fees, outstanding interest, and prepayment penalty fees, which resulted in a $2.2 million loss on extinguishment of debt in the quarter ended March 31, 2018.

The estimated fair value of the debt (categorized as a Level 2 liability for fair value measurement purposes) is determined using current market factors and the ability of the Company to obtain debt at comparable terms to those that are currently in place. As of December 31, 2019 and 2018, the fair value of the Company's debt approximated the carrying amount.

Interest Expense

Interest expense related to debt and the finance lease for the years ended December 31, 2019, 2018, and 2017, which includes the contractual interest coupon payable semi-annually in cash, the amortization of the issuance costs, and accretion of debt discount is as follows (in thousands):

	Years ended December 31,		
	2019	2018	2017
Contractual interest expense	$ 7,883	$ 8,183	$ 5,149
Amortization of debt issuance costs	1,397	1,350	118
Accretion of back-end fee on debt	—	50	658
Accretion of debt discount	17,985	15,889	—
Total convertible debt interest expense	$ 27,265	$ 25,472	$ 5,925
Finance lease interest expense	440	—	—
Total interest expense	$ 27,705	$ 25,472	$ 5,925

9. Shareholders' Equity

Common Stock—As of December 31, 2019, the Company had 500,000,000 shares of common stock authorized with a par value of $0.01 and 89,682,387 shares of common stock issued and outstanding. In addition, as of December 31, 2019, the Company had reserved 10,492,946 shares of common stock for issuance upon the exercise of outstanding common stock options and 500,822 shares of common stock for issuance upon the vesting of restricted stock units.

In the second quarter of 2019, the Company completed an underwritten public offering of 10,657,692 shares of the Company's common stock, which included the underwriters' exercise in full of their over-allotment option of 1,042,307 shares from the Company at a price to the public of $26.00, less underwriting discounts and commissions. The Company's net proceeds from the sale of the shares, after deducting the underwriting discounts and commissions and offering expenses of $16.0 million, were $261.1 million. The offering also included the sale of 400,000 shares from the Company's Chairman and Chief Executive Officer, from which the Company received no proceeds.

9. Shareholders' Equity (Continued)

In January 2018, the Company 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. The fair value of the liability component of the Convertible Notes on the date of issuance was estimated at $309.1 million, and accordingly, the equity component (included in additional paid-in capital) on the date of issuance was calculated as $140.9 million using the residual method, as further described in Note 8 Debt.

In September 2017, the Company completed an underwritten public offering of 14,123,150 shares of the Company's 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. The Company's net proceeds from the sale of the shares, after deducting underwriting discounts and offering expenses of $24.8 million, were approximately $377.7 million.

Preferred Stock—As of December 31, 2019 and 2018, the Company had 200,000,000 shares of preferred stock authorized with a par value of $0.01 and no shares of preferred stock were issued and outstanding.

10. Stock-Based Compensation

The Company's current equity compensation plan, the 2019 Incentive Plan, was approved by shareholders at the Company's Annual Meeting of Shareholders in May 2019. The 2019 Incentive Plan is administered by the Compensation Committee of the Board of Directors of the Company. Under the terms of the 2019 Incentive Plan, the Company is authorized to grant a variety of incentive awards based on its common stock, including stock options (both incentive stock options and non-qualified stock options), RSUs, performance options/shares and other stock awards to eligible employees and non-employee directors. Upon the approval of the 2019 Incentive Plan by shareholders, 3,500,000 shares were authorized for issuance thereunder, plus any shares subject to then-outstanding awards under the 2017 Incentive Plan, 2015 Incentive Plan and the 2013 Incentive Plan that subsequently were canceled, terminated unearned, expired, were forfeited, lapsed for any reason or were settled in cash without the delivery of shares. As of December 31, 2019, 3,868,698 shares remained for future issuance under the 2019 Incentive Plan. The 2019 Incentive Plan will terminate on May 16, 2029 unless it is extended or terminated earlier pursuant to its terms. In addition, from time to time, the Company makes inducement grants of stock options. These awards are made pursuant to the Nasdaq inducement grant exception as a component of new hires' employment compensation in connection with the Company's equity grant program. During the twelve months ended December 31, 2019 and 2018, the Company granted inducement stock options covering 305,180 and 295,720 shares, respectively, of the Company's common stock to new employees.

Stock Options—The Company calculates the fair value of stock options granted using the Black-Scholes valuation model. The following table summarizes the grant date fair value and assumptions used in determining the fair value of all stock options granted, including grants of inducement options, during the years ended December 31, 2019, 2018 and 2017.

	2019	2018	2017
Volatility	67%-70%	66% - 68%	71% - 79%
Risk-free interest rate	1.35%-2.56%	2.25% - 2.96%	1.73% - 2.13%
Dividend yield	0.0%	0.0%	0.0%
Expected option term (in years)	5.09	5.09	6.25
Weighted average fair value of stock options granted	$8.76	$16.03	$10.52

For the years ended December 31, 2019, 2018 and 2017, the volatility factor was based on the Company's historical volatility during the expected option term. Estimated forfeitures were based on the actual percentage of option forfeitures since the closing of the Company's merger with Transave, Inc. in December 2010 for the years ended 2017 and prior. Beginning with the year ended December 31, 2018, estimated forfeitures were based on the actual percentage of option forfeitures over the expected option term.

From time to time, the Company grants performance-condition options to certain employees. Vesting of these options is subject to the Company achieving certain performance criteria established at the date of grant and the individuals fulfilling a service condition (continued employment). As a result of the FDA approval of ARIKAYCE in September 2018, the vesting of

10. Stock-Based Compensation (Continued)

performance options totaling $1.1 million was recorded as noncash compensation expense in the third quarter of 2018. The Company had no performance options outstanding as of December 31, 2019 and 2018.

The following table summarizes stock option activity for stock options granted for the years ended December 31, 2019, 2018 and 2017 as follows:

	Number of Shares	Weighted Average Exercise Price	Weighted Average Remaining Contractual Life in Years	Aggregate Intrinsic Value (in '000)
Options outstanding at January 1, 2017	7,116,706	$ 13.30		
Granted	2,284,710	$ 15.92		
Exercised	(378,275)	$ 9.08		
Forfeited and expired	(414,220)	$ 15.50		
Options outstanding at December 31, 2017	8,608,921	$ 14.08		
Vested and expected to vest at December 31, 2017	8,325,255	$ 14.03		
Exercisable at December 31, 2017	4,229,478	$ 12.71		
Options outstanding at December 31, 2017	8,608,921	$ 14.08		
Granted	1,755,600	$ 27.63		
Exercised	(494,351)	$ 14.46		
Forfeited and expired	(488,440)	$ 19.79		
Options outstanding at December 31, 2018	9,381,730	$ 16.30		
Vested and expected to vest at December 31, 2018	8,693,635	$ 15.90		
Exercisable at December 31, 2018	5,649,698	$ 13.45		
Granted	3,434,270	$ 15.02		
Exercised	(1,413,341)	$ 11.87		
Forfeited and expired	(909,713)	$ 19.02		
Options outstanding at December 31, 2019	10,492,946	$ 16.24	6.82	$ 86,921
Vested and expected to vest at December 31, 2019	9,767,035	$ 16.15	6.67	$ 81,572
Exercisable at December 31, 2019	5,719,818	$ 15.38	5.37	$ 51,000

The total intrinsic value of stock options exercised during the years ended December 31, 2019, 2018 and 2017 was $16.5 million, $5.6 million and $4.3 million, respectively.

As of December 31, 2019, there was $31.1 million of unrecognized compensation expense related to unvested stock options, which is expected to be recognized over a weighted average period of 2.6 years. The following table summarizes the range of exercise prices and the number of stock options outstanding and exercisable as of December 31, 2019:

10. Stock-Based Compensation (Continued)

Outstanding as of December 31, 2019				Exercisable as of December 31, 2019	
Range of Exercise Prices	Number of Options	Weighted Average Remaining Contractual Term (in Years)	Weighted Average Exercise Price	Number of Options	Weighted Average Exercise Price
$ 3.03 – $ 10.85	1,419,872	4.63	$ 7.55	1,311,142	$ 7.27
$ 11.14 – $ 13.67	1,547,063	5.44	$ 12.91	1,237,855	$ 12.76
$ 13.91 – $ 13.91	2,661,040	9.01	$ 13.91	—	$ —
$ 13.94 – $ 16.16	1,394,176	5.57	$ 15.59	1,180,091	$ 15.56
$ 16.44 – $ 19.47	1,112,775	7.16	$ 17.75	696,563	$ 17.88
$ 19.65 – $ 24.22	1,139,884	6.04	$ 22.29	892,465	$ 22.25
$ 24.41 – $ 30.46	1,058,332	8.20	$ 29.12	339,295	$ 29.46
$ 30.86 – $ 31.73	131,180	8.09	$ 30.94	48,407	$ 30.96
$ 31.78 – $ 31.78	21,794	7.48	$ 31.78	11,439	$ 31.78
$ 32.46 – $ 32.46	6,830	8.00	$ 32.46	2,561	$ 32.46

Restricted Stock and Restricted Stock Units—The Company may grant Restricted Stock (RS) and Restricted Stock Units (RSUs) to employees and non-employee directors. Each share of RS vests upon and each RSU represents a right to receive one share of the Company's common stock upon the completion of a specific period of continued service.

RS and RSU awards granted are valued at the market price of the Company's common stock on the date of grant. The Company recognizes noncash compensation expense for the fair values of these RS and RSUs on a straight-line basis over the requisite service period of these awards.

The following table summarizes RSU awards granted during the years ended December 31, 2019, 2018 and 2017:

	Number of RSUs	Weighted Average Grant Price
Outstanding at January 1, 2017	89,194	$ 10.85
Granted	46,914	$ 17.16
Released	(89,194)	$ 10.85
Forfeited	—	$ —
Outstanding at December 31, 2017	46,914	$ 17.16
Granted	253,586	$ 29.16
Released	(51,992)	$ 18.46
Forfeited	(20,682)	$ 29.05
Outstanding at December 31, 2018	227,826	$ 29.14
Granted	407,655	$ 27.89
Released	(92,145)	$ 28.05
Forfeited	(42,514)	$ 29.11
Outstanding at December 31, 2019	500,822	$ 28.32

10. Stock-Based Compensation (Continued)

As of December 31, 2019, there was $8.3 million of unrecognized compensation expense related to unvested awards, which is expected to be recognized over a weighted average period of 2.7 years.

The following table summarizes the stock-based compensation recorded in the consolidated statements of comprehensive loss related to stock options and RSUs during the years ended December 31, 2019, 2018 and 2017 (in millions):

	2019	2018	2017
Research and development expenses	$ 8.2	$ 9.4	$ 6.5
Selling, general and administrative expenses	18.8	16.8	11.6
Total	$ 27.0	$ 26.2	$ 18.1

Employee Stock Purchase Plan - On May 15, 2018, the Company's shareholders approved the Company's 2018 Employee Stock Purchase Plan (ESPP). As part of the ESPP, eligible employees may acquire an ownership interest in the Company by purchasing common stock, at a discount, through payroll deductions. The ESPP is compensatory under GAAP and the Company recorded stock compensation expense of $1.6 million and $0.9 million for the years ended December 31, 2019 and 2018, respectively.

11. Income Taxes

The income tax provision (benefit) was $0.8 million, $0.2 million and $(0.3) million and the effective rates were approximately 0%, 0% and 0% for the years ended December 31, 2019, 2018 and 2017, respectively. 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 the Company paid in 2009. As a result of the Tax Cuts and Jobs Act (the Tax Act), the Company recorded a noncurrent receivable to reflect the refund due to the Company in future periods relating to the previously paid AMT. In addition, the income tax provision (benefit) for the years ended December 31, 2019, 2018 and 2017 reflected current income tax expense recorded as a result of the taxable income in certain of the Company's non-US subsidiaries.

For the years ended December 31, 2019 and 2018, the Company was also subject to foreign income taxes as a result of legal entities established for activities in Europe and Japan. The Company's loss before income taxes in the US and globally was as follows (in thousands):

	Years Ended December 31,		
	2019	2018	2017
US	$ (201,161)	$ (286,211)	$ (136,682)
Foreign	(52,399)	(37,865)	(56,239)
Total	$ (253,560)	$ (324,076)	$ (192,921)

11. Income Taxes (Continued)

The Company's income tax provision (benefit) consisted of the following (in thousands):

	Years Ended December 31,		
	2019	2018	2017
Current:			
Federal	$ —	$ —	$ —
State	10	4	3
Foreign	767	197	142
	777	201	145
Deferred:			
Federal	—	—	(417)
State	—	—	—
Foreign	—	—	—
	—	—	(417)
Total	$ 777	$ 201	$ (272)

The reconciliation between the federal statutory tax rates and the Company's effective tax rate is as follows:

	Years Ended December 31,		
	2019	2018	2017
Statutory federal tax rate	21 %	21 %	34 %
Permanent items	(1)%	— %	(3)%
State income taxes, net of federal benefit	6 %	5 %	4 %
R&D and other tax credits	2 %	2 %	8 %
Foreign income taxes	1 %	(1)%	(6)%
Impact of Tax Act	— %	— %	(49)%
Change in valuation allowance	(32)%	(27)%	12 %
Change in Irish trading status	3 %	— %	— %
Effective tax rate	— %	— %	— %

The trading income tax rate for an Irish company is 12.5% and the non-trading income tax rate is 25%. During 2019, the Company determined that it qualifies as a non-trading company. As such, the Company's Irish NOLs were revalued to the

11. Income Taxes (Continued)

higher rate. Further, not all expenses incurred will result in a non-trading company loss carryforward. These changes had no impact to income tax expense as a result of the valuation allowance.

Deferred tax assets and liabilities are determined based on the difference between financial statement and tax bases using enacted tax rates in effect for the year in which the differences are expected to reverse. The components of the deferred tax assets and liabilities consist of the following:

	As of December 31,	
	2019	2018
Deferred tax assets:		
Net operating loss carryforwards	$ 300,292	$ 231,918
General business credits	114,887	109,502
Product license	6,456	6,902
Inventory	3,129	7,651
Stock based compensation	20,587	17,960
Other	10,012	6,895
Deferred tax assets	$ 455,363	$ 380,828
Deferred tax liabilities:		
Intangibles	$ (14,316)	$ (15,424)
Convertible debt	(27,570)	(32,799)
Deferred tax liabilities	$ (41,886)	$ (48,223)
Net deferred tax assets	$ 413,477	$ 332,605
Valuation allowance	(413,477)	(332,605)
Net deferred tax assets	$ —	$ —

The net deferred tax assets (prior to applying the valuation allowance) of $413.5 million and $332.6 million at December 31, 2019 and 2018, respectively, primarily consist of net operating loss carryforwards for income tax purposes. Due to the Company's history of operating losses, the Company recorded a valuation allowance on its net deferred tax assets by increasing the valuation allowance by $80.9 million and $71.3 million in 2019 and 2018, respectively, as it was more likely than not that such tax benefits will not be realized.

At December 31, 2019, the Company had federal net operating loss carryforwards for income tax purposes of approximately $1.1 billion. Due to the limitation on NOLs as more fully discussed below, $889.0 million of the NOLs are available to offset future taxable income, if any. The NOL carryovers and general business tax credits expire in various years beginning in 2018. For state tax purposes, the Company has approximately $517.4 million of New Jersey NOLs available to offset against future taxable income. The Company also has California and Virginia NOLs that are entirely limited due to Section 382 (as discussed below). The Company has $152.4 million of non-trading loss carryforwards for Irish tax purposes.

From 2014 through 2017, the Company completed an Internal Revenue Code Section 382 (Section 382) analysis in order to determine the amount of losses that are currently available for potential offset against future taxable income, if any. It was determined that the utilization of the Company's NOL and general business tax credit carryforwards generated in tax periods up to and including December 2010 were subject to substantial limitations under Section 382 due to ownership changes that occurred at various points from the Company's original organization through December 2010. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of shareholders that own, directly or indirectly, 5% or more of a corporation's stock, in the stock of a corporation by more than 50 percentage points over a testing period (usually 3 years). Since the Company's formation in 1999, it has raised capital through the issuance of common stock on several occasions which, combined with the purchasing shareholders' subsequent disposition of those shares, have resulted in multiple changes in ownership, as defined by Section 382. These ownership changes resulted in substantial limitations on the use of the Company's NOLs and general business tax credit carryforwards up to and including December 2010. The Company

11. Income Taxes (Continued)

continues to track all of its NOLs and tax credit carryforwards but has provided a full valuation allowance to offset those amounts.

On December 22, 2017, the US government enacted the Tax Act. The Tax Act significantly revises US tax law by, among other provisions, lowering the US federal statutory income 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

ASC 740, *Income Taxes* requires the effects of changes in tax laws to be recognized in the period in which the legislation is enacted. However, due to the complexity and significance of the Tax Act's provisions, the SEC staff issued SAB 118, which allowed companies to record the tax effects of the Tax Act on a provisional basis based on a reasonable estimate, and then, if necessary, subsequently adjust such amounts during a limited measurement period as more information becomes available.

The Tax Act did not have a material impact on the Company's financial statements because its deferred temporary differences are fully offset by a valuation allowance and the Company does not have any significant offshore earnings from which to record the mandatory transition tax. The Company completed its analysis during the fourth quarter of 2018 and no additional tax effects of the Act were required to be recorded for the year ended December 31, 2018.

The financial statement recognition of the benefit for a tax position is dependent upon the benefit being more likely than not to be sustainable upon audit by the applicable taxing authority. If this threshold is met, the tax benefit is then measured and recognized at the largest amount that is greater than 50% likely of being realized upon ultimate settlement. If such unrecognized tax benefits were realized and not subject to valuation allowances, the Company would recognize a tax benefit of $4.8 million. The following table summarizes the gross amounts of unrecognized tax benefits (in thousands):

	2019	2018
Balance as of January 1,	$ 4,087	$ —
Additions related to prior period tax positions	—	3,345
Reductions related to prior period tax positions	(60)	—
Additions related to current period tax positions	809	742
Balance as of December 31,	$ 4,836	$ 4,087

The Company is subject to US federal and state income taxes and the statute of limitations for tax audit is open for the federal tax returns for the years ended 2016 and later, and is generally open for certain states for the years 2015 and later. The Company has incurred net operating losses since inception, except for the year ended December 31, 2009. Such loss carryforwards would be subject to audit in any tax year in which those losses are utilized, notwithstanding the year of origin.

The Company's policy is to recognize interest accrued related to unrecognized tax benefits and penalties in income tax expense. The Company has recorded no such expense. As of December 31, 2019 and 2018, the Company has recorded reserves for unrecognized income tax benefits of $4.8 million and $4.1 million, respectively. As any adjustment to the Company's uncertain tax positions would not result in a cash tax liability, it has not recorded any accrued interest or penalties related to its uncertain tax positions. The Company does not anticipate any material changes in the amount of unrecognized tax positions over the next 12 months.

12. License and Other Agreements

In-License Agreements

PARI Pharma GmbH—In April 2008, the Company entered into a licensing agreement with PARI Pharma GmbH (PARI) for use of the optimized Lamira Nebulizer System for delivery of ARIKAYCE in treating patients with NTM lung infections, CF and bronchiectasis. Under the licensing agreement, the Company has rights under several US and foreign issued

12. License and Other Agreements (Continued)

patents and patent applications involving improvements to the optimized Lamira Nebulizer System, to exploit the system with ARIKAYCE for the treatment of such indications, but the Company cannot manufacture the nebulizers except as permitted under the a commercialization agreement with PARI, which is described in further detail below. The Lamira Nebulizer System has been approved for use in the US (in combination with ARIKAYCE) and EU. Under the licensing agreement, the Company paid PARI an upfront license fee and certain milestone payments. Upon FDA acceptance of the Company's New Drug Application and the subsequent FDA approval of ARIKAYCE, the Company paid PARI additional milestone payments of €1.0 million and €1.5 million, respectively. In addition, PARI is entitled to receive a future milestone payment of €0.5 million in cash based first receipt of the first marketing approval in a major EU country for ARIKAYCE and the device. In October 2017, the Company exercised an option to buy-down the royalties that will be paid to PARI on ARIKAYCE net sales. As a result, PARI is 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. The buy-down payment to PARI was included as a component of SG&A expenses in the fourth quarter of 2017. See below for information related to the commercialization agreement with PARI.

Other Agreements

Cystic Fibrosis Foundation Therapeutics, Inc.—In 2004 and 2009, the Company entered into research funding agreements with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) whereby it received $1.7 million and $2.2 million in research funding for the development of ARIKAYCE. As a result of the US approval of ARIKAYCE and in accordance with the agreements, as amended, the Company owes payments to CFFT of $13.4 million in the aggregate, which are payable through 2025. Furthermore, if certain global sales milestones are met within five years of the ARIKAYCE's commercialization, the Company would owe up to an additional $3.9 million. The Company has determined the likelihood of meeting such global sales milestones and have accrued for these contingent obligations proportionally based on net sales of ARIKAYCE.

Therapure Biopharma Inc.—In February 2014, the Company entered into a contract manufacturing agreement with Therapure Biopharma Inc. (Therapure) for the manufacture of ARIKAYCE, on a non-exclusive basis, at a 200 kg scale. Pursuant to the agreement, the Company and Therapure collaborated to construct a production area for the manufacture of ARIKAYCE in Therapure's existing manufacturing facility in 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, the Company is obligated to pay a minimum of $6 million for commercial ARIKAYCE batches produced and certain manufacturing activities each calendar year.

PARI Pharma GmbH—In July 2014, the Company entered into a commercialization agreement with PARI (the Commercialization Agreement) 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 the Company 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 fifteen years from the first commercial sale of ARIKAYCE in October 2018 (the Initial Term). The term of the agreement may be extended by the Company for an additional five years by providing written notice to PARI at least one year prior to the expiration of the Initial Term. Notwithstanding the foregoing, the parties have certain rights and obligations under the agreement prior to the commencement of the Initial Term.

Ajinomoto Althea, Inc.—In September 2015, the Company entered into a Commercial Fill/Finish Services Agreement (the Fill/Finish Agreement) with Ajinomoto Althea, Inc., a Delaware corporation (Althea), for Althea to produce, on a non-exclusive basis, ARIKAYCE in finished dosage form at a 50 kg scale. Under the Fill/Finish Agreement, the Company is 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, is expected to 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. The Company has expensed at least the required minimum in each year of the contract.

AstraZeneca AB—In October 2016, the Company entered into a license agreement (AZ License Agreement) with AstraZeneca AB, a Swedish corporation (AstraZeneca). Pursuant to the terms of the AZ License Agreement, AstraZeneca granted the Company exclusive global rights for the purpose of developing and commercializing AZD7986 (renamed INS 1007). In consideration of the licenses and other rights granted by AstraZeneca, the Company made an upfront payment of

12. License and Other Agreements (Continued)

$30.0 million, which was included as research and development expense in the fourth quarter of 2016. The Company is also obligated to make a series of contingent milestone payments totaling up to an additional $85.0 million upon the achievement of clinical development and regulatory filing milestones. If the Company elects to develop INS1007 for a second indication, the Company will be obligated to make an additional series of contingent milestone payments to AstraZeneca totaling up to $42.5 million. The Company is not obligated to make any additional milestone payments for additional indications. In addition, the Company will 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 $1.0 billion in annual net sales. The AZ License Agreement provides AstraZeneca with the option to negotiate a future agreement with the Company for commercialization of INS1007 in chronic obstructive pulmonary disease or asthma.

Patheon UK Limited—In October 2017, the Company entered into certain agreements with Patheon UK Limited (Patheon) related to the increase of its long-term production capacity for ARIKAYCE commercial inventory. The agreements provide for Patheon to manufacture and supply ARIKAYCE for its anticipated commercial needs. Under these agreements, the Company is 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 commence once certain technology transfer and construction services are completed. The Company's 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 party has 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 to increase our long-term production capacity, 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.

13. Commitments and Contingencies

Commitments

In September 2018, the Company entered into a lease for its new corporate headquarters in Bridgewater, New Jersey. The initial lease term commenced in October 2019 and expires in September 2030. In July 2016, the Company signed an operating lease for laboratory space, also located in Bridgewater, for which the initial lease term expires in September 2021. In October 2018, the Company expanded its lease for laboratory space located in Bridgewater, which commenced in January 2019. Future minimum rental payments under the Bridgewater leases are $34.5 million.

Rent expense charged to operations was $3.2 million, $2.1 million, and $1.5 million for the years ended December 31, 2019, 2018 and 2017, respectively. Rent expense is recorded on a straight-line basis over the term of the applicable leases.

In addition to rent, the Company has several firm purchase commitments, primarily related to the manufacturing of ARIKAYCE and annual minimum royalties on global net sales of ARIKAYCE. Future firm purchase commitments under these agreements, the last of which ends in 2034, total $82.0 million. These amounts do not represent the Company's entire anticipated purchases in the future, but instead represent only purchases that are the subject of contractually obligated minimum purchases. The minimum commitments disclosed are determined based on non-cancelable minimum spend amounts or termination amounts. Additionally, the Company purchases products and services as needed with no firm commitment.

Legal Proceedings

From time to time, the Company is 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 the Company’s consolidated financial position, results of operations or cash flows.

14. Retirement Plan

The Company has a 401(k) defined contribution plan for the benefit for all US employees and permits voluntary contributions by employees subject to IRS-imposed limitations. Effective January 1, 2018, the Company matched 100% of eligible employee contributions on the first 4% of employee salary (up to the IRS maximum). Employer contributions for the

14. Retirement Plan (Continued)

year ended December 31, 2019, 2018 and 2017 were $2.8 million, $2.2 million and $0.8 million, respectively. In 2017, the Company matched 100% of eligible employee contributions on the first 3% of employee salary (up to the IRS maximum).

15. Quarterly Financial Data (Unaudited)

The following table summarizes unaudited quarterly financial data for the years ended December 31, 2019 and 2018 (in thousands, except per share data).

	2019				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
Revenues	$ 21,902	$ 29,972	$ 38,885	$ 45,708	$ 136,467
Gross profit*	$ 17,752	$ 25,053	$ 32,448	$ 37,002	$ 112,255
Operating loss	$ (69,509)	$ (62,166)	$ (56,488)	$ (47,082)	$ (235,245)
Net loss	$ (74,153)	$ (66,514)	$ (60,682)	$ (52,988)	$ (254,337)
Basic and diluted net loss per share	$ (0.96)	$ (0.81)	$ (0.68)	$ (0.59)	$ (3.01)

	2018				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter**	Total
Revenues	$ —	$ —	$ —	$ 9,835	$ 9,835
Gross profit*	$ —	$ —	$ —	$ 7,412	$ 7,412
Operating loss	$ (62,751)	$ (72,882)	$ (83,983)	$ (87,722)	$ (307,338)
Net loss	$ (68,524)	$ (76,437)	$ (87,743)	$ (91,573)	$ (324,277)
Basic and diluted net loss per share	$ (0.89)	$ (1.00)	$ (1.14)	$ (1.19)	$ (4.22)

* Excludes amortization of intangible assets.

Basic and diluted net loss per share amounts included in the above table were computed independently for each of the quarters presented. Accordingly, the sum of the quarterly basic and diluted net loss per share amounts may not agree to the total for the year.

Paving stones outside Insmed's global headquarters in New Jersey showcase employees' personal motivations for serving the rare disease community.

EXECUTIVE COMMITTEE

William H. Lewis, J.D., M.B.A.
Chairman and
Chief Executive Officer

Roger Adsett, M.B.A.
Chief Operating Officer

Sara M. Bonstein, M.B.A.
Chief Financial Officer

Martina Flammer, M.D., M.B.A.
Chief Medical Officer

Christine Pellizzari, J.D.
Chief Legal Officer

S. Nicole Schaeffer, M.B.A.
Chief People Strategy Officer

John D. Soriano, J.D.
Chief Compliance Officer

Eugene J. Sullivan, M.D.
Chief Product Strategy Officer

BOARD OF DIRECTORS

William H. Lewis, J.D., M.B.A.
Chairman and Chief Executive Officer, Insmed Incorporated

David R. Brennan[3]
Lead Independent Director, Insmed Incorporated
Former Chief Executive Officer, AstraZeneca PLC

Elizabeth McKee Anderson[2]
Former Worldwide Vice President, Global Strategic Marketing and Market Access, Infectious Diseases and Vaccines, Janssen Pharmaceuticals, Inc.

Alfred F. Altomari[1,3]
Chairman and Chief Executive Officer, Agile Therapeutics, Inc. (Nasdaq: AGRX)

Clarissa Desjardins, Ph.D.[4]
Former President and Chief Executive Officer, Clementia Pharmaceuticals, Inc. (now Ipsen S.A.)

Steinar J. Engelsen, M.D.[1, 4]
Former Acting
Chief Executive Officer,
Centaur Pharmaceuticals, Inc.

Leo Lee[3,4]
Chief Executive Officer and Executive Director, Regeneus (ASX: RGS)

David W.J. McGirr[1]
Former Chief Financial Officer, Cubist Pharmaceuticals, Inc. (now Merck & Co., Inc.)

Melvin Sharoky, M.D.[2, 4]
Former President and Chief Executive Officer, Somerset Pharmaceuticals, Inc.

Committee Legend (bold indicates chairperson) 1: Audit; 2: Nomination & Governance; 3: Compensation; 4: Science & Technology

Shareholders may receive without charge a copy of our Annual Report on Form 10-K for the year ended December 31, 2019 by going to investor.insmed.com or by sending a written request to Ms. Christine Pellizzari, Corporate Secretary, Insmed Incorporated, 700 US Highway 202/206, Bridgewater, New Jersey, 08807, (908) 977-9900. In connection with any such request, we will provide a list of exhibits to the Annual Report on Form 10-K for the year ended December 31, 2019, and will provide copies of any such exhibit upon the payment of a reasonable fee.

GLOBAL HEADQUARTERS
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TRADING SYMBOL
The common stock of Insmed Incorporated is listed on the Nasdaq Global Select Market under the symbol INSM.

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ANNUAL SHAREHOLDER MEETING
To be held on Tuesday, May 12, 2020, 9:00 a.m.

www.insmed.com

Various statements in this annual report are "forward-looking statements," as that term is defined in the Private Securities Litigation Reform Act of 1995. 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. For additional information, see Item 1A – Risk Factors of the Form 10-K included in this Annual Report. We undertake no obligation to update or revise publicly any forward-looking statements.