TETRAPHASE PHARMACEUTICALS INC
Form 10-K
March 15, 2019

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, 2018

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: 001-35837

TETRAPHASE PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	04-3581650
(State or Other Jurisdiction of	(I.R.S. Employer
Incorporation or Organization)	Identification No.)

480 Arsenal Way

Watertown, Massachusetts 02472

(Address of Principal Executive Offices) (zip code)

Registrant’s telephone number, including area code: (617) 715-3600

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

Title of each class	Name of each exchange on which registered
Common Stock, $.001 par value	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

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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See 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 registrant's common stock, $0.001 par value per share ("Common Stock"), held by non-affiliates of the registrant, based on the last reported sale price of the Common Stock on the Nasdaq Global Select Market at the close of business on June 30, 2018, was $179,056,120. For purposes hereof, shares of Common Stock held by each executive officer and director of the registrant and entities affiliated with such executive officers and directors have been excluded from the foregoing calculation because such persons and entities may be deemed to be

affiliates of the registrant. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares outstanding of the registrant's Common Stock as of March 12, 2019: 53,745,497

Documents incorporated by reference:

Portions of our definitive proxy statement for our 2019 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

TETRAPHASE PHARMACEUTICALS, INC.

TABLE OF CONTENTS

References to Tetraphase

Throughout this Annual Report on Form 10-K, the "Company," "Tetraphase," "we," "us," and "our," except where the context requires otherwise, refer to Tetraphase Pharmaceuticals, Inc. and its consolidated subsidiaries, and "our board of directors" refers to the board of directors of Tetraphase Pharmaceuticals, Inc.

The Tetraphase Pharmaceuticals™ name and logo and the Xerava™ name and logo are registered trademarks of trade names of Tetraphase Pharmaceuticals, Inc. in the United States and/or other countries. trademarks, trade names and service marks appearing in this Annual Report on Form 10-K are the property of their respective owners.

Forward-Looking Information

This Annual Report on Form 10-K contains forward-looking statements regarding, among other things, our future discovery and development efforts, our future operating results and financial position, our business strategy, and other objectives for our operations. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "pro "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. You also can identify them by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause our actual results to differ materially from those indicated by forward-looking statements. These risks and uncertainties include those inherent in pharmaceutical research and development and the commercialization of pharmaceuticals, such as our ability to successfully commercialize Xerava, decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our drug candidates, adverse results in our drug discovery and clinical development activities, our ability to obtain, maintain and enforce intellectual property rights for our drug candidates, our ability to obtain any necessary financing to conduct our planned activities, and other risk factors. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in the section entitled "Risk Factors" in Part I that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make. Unless required by law, we do not undertake any obligation to publicly update any forward-looking statements.

PART I

ITEM 1. Business

Overview

We are a biopharmaceutical company using our proprietary chemistry technology to create, develop and commercialize novel tetracyclines for serious and life-threatening conditions, including bacterial infections caused by multidrug-resistant, or MDR, bacteria. There is a medical need for new antibiotics as resistance to existing antibiotics increases. In recognition of this need, we developed our product, Xerava™ (eravacycline), a fully synthetic fluorocycline, as an intravenous, or IV antibiotic for use as a first-line empiric monotherapy for the treatment of MDR infections, including MDR Gram-negative infections, such as those found in complicated intra-abdominal infections, or cIAI.

On August 27, 2018, the United States Food and Drug Administration, or FDA, approved Xerava for the treatment of cIAI in adults. Approval of Xerava was based on our IGNITE (Investigating Gram-Negative Infections Treated with Eravacycline) phase 3 program. In the first pivotal phase 3 trial in the IGNITE program in patients with cIAI, twice-daily IV Xerava met the primary endpoint by demonstrating statistical non-inferiority of clinical response compared to ertapenem, a carbapenem and a standard of care treatment for cIAI, and was well-tolerated. We refer to this trial as IGNITE1. In our other pivotal phase 3 clinical trial of Xerava in patients with cIAI, twice-daily IV Xerava met the primary endpoint by demonstrating statistical non-inferiority of clinical response compared to meropenem, another standard of care treatment, and was well-tolerated. We refer to this trial as IGNITE4. In both IGNITE1 and IGNITE4, Xerava achieved high cure rates in patients with poly-microbial infections (Gram-negative, Gram-positive, and anaerobic infections), including resistant isolates.

In October 2018, we commenced sales of Xerava in the United States. We are commercializing Xerava in the United States using a small, targeted commercial and medical affairs groups to build and promote access to Xerava. As a result, as of March 1, 2019, we have approximately 40 sales representatives in the field, three strategic market access executives and approximately 10 medical affairs personnel supporting Xerava in the United States.

On September 20, 2018, based on the results of IGNITE1, the European Commission, or EC, granted marketing authorization for Xerava for the treatment of cIAI in adults in all 28 countries of the European Union, or EU, plus Norway, Iceland and Liechtenstein. In February 2018 we entered into a license agreement with Everest Medicines Limited, or Everest Medicines, granting Everest Medicines commercialization rights to eravacycline in China and other Asian territories. In June 2018, Everest Medicines submitted an Investigational New Drug, or IND, application to the China National Medical Products Administration (formerly China FDA) for a phase 3 clinical trial of eravacycline in cIAI. The application was approved, and Everest Medicines expects to begin enrolling patients in this phase 3 trial in the second quarter of 2019.

Subject to obtaining additional financing, we intend to pursue development of Xerava for the treatment of additional indications, including other serious and life-threatening infections. We may pursue these development activities either by ourselves or with collaborators.

We believe that the ability of Xerava to cover MDR Gram-negative bacteria, as well as MDR Gram-positive, anaerobic and atypical bacteria, may enable Xerava to become the drug of choice for first-line empiric treatment of patients with cIAI. In in vitro studies, Xerava has demonstrated the ability to cover a wide variety of MDR

Gram-negative, Gram-positive, anaerobic and atypical bacteria, including multidrug-resistant Klebsiella pneumoniae and MDR Acinetobacter. Multidrug-resistant Klebsiella pneumoniae is one of the carbapenem-resistant Enterobacteriaceae (or CREs) listed as an urgent threat and MDR Acinetobacter is listed as a serious threat by the Centers for Disease Control and Prevention, or CDC, in a September 2013 report. They are also listed as “Priority 1; Critical Pathogens” in the World Health Organization’s priority pathogens list for R&D, published in February 2017. CREs were a confirmed area of great concern by the World Health Organization in an April 2014 global surveillance report. Gram-negative bacteria that are resistant to multiple available existing antibiotics are increasingly common and a growing threat to public health.

In addition to Xerava we are also developing other fluorocycline antibiotic compounds, TP-6076 and TP-271, and TP-2846, a tetracycline for the treatment of acute myeloid leukemia. We are developing TP-6076, a fully-synthetic fluorocycline derivative, as a lead candidate under our second-generation program to target unmet medical needs, including MDR Gram-negative bacteria such as carbapenem-resistant Enterobacteriaceae and carbapenem-resistant Acinetobacter baumanii. To date, we have conducted phase 1 single- and multiple-ascending dose studies evaluating the safety, tolerability and pharmacokinetics of IV TP-6076 in healthy volunteers. We are currently conducting a Phase 1 study to assess the bronchopulmonary disposition, pharmacokinetics, and safety of TP-6076 in healthy volunteers. TP-271 is a fully-synthetic fluorocycline that we are developing for respiratory disease caused by bacterial biothreat and antibiotic-resistant public health pathogens, as well as bacterial pathogens associated with community-acquired bacterial pneumonia. To date, we have completed single- and multiple-ascending dose trials for IV and oral formulations of TP-271. We expect to report results of these studies at a future scientific meeting. In February 2017, we received Qualified Infectious Disease Product and Fast Track designations from the FDA for TP-271. To continue the development of TP-271 we are looking to secure additional non-dilutive funding. We are also developing TP-2846, a fully-synthetic tetracycline discovered in-house, for the treatment of acute myeloid leukemia, or AML. We have recently initiated pre-clinical toxicology studies for this compound and will present preclinical data at the 2019 American Association for Cancer Research conference.

In 2011 and 2012, the United States government awarded contracts for potential funding of over $100 million for the development of our antibiotic compounds, Xerava, TP-6076 and TP-271. These awards include a contract for up to $67.3 million from the Biomedical Advanced Research and Development Authority, or BARDA, an agency of the U.S. Department of Health and Human Services, for the development of Xerava for the treatment of disease caused by bacterial biothreat pathogens. We refer to this contract as the BARDA Contract. These awards also include a contract for up to $35.8 million from the National Institute of Allergy and Infectious Diseases, or NIAID, a division of the National Institutes of Health, for the development of TP-271. We refer to this contract as the NIAID Contract. In addition, during 2011, NIAID awarded a separate grant for $2.9 million. We refer to this award as the NIAID Grant. These awards were made to CUBRC, Inc., or CUBRC, an independent, not-for-profit, research corporation that specializes in U.S. government-based contracts, with which we are collaborating. CUBRC serves as the prime contractor under these awards, primarily carrying out a program management and administrative role with additional responsibility for the management of preclinical studies. We served as lead technical expert on all aspects of these awards and also served as a subcontractor of CUBRC responsible for management of chemistry, manufacturing and control activities and clinical studies.

In March 2017, the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, an international public-private partnership focused on advancing new antimicrobial products to address the threat of antibiotic resistance, selected us to receive up to $4.0 million in research funding over 18 months for TP-6076. In connection with this funding, we entered into a cost reimbursement Sub-Award Agreement with the Trustees of Boston University, the administrator of the program. We began recognizing revenue from the Sub-Award Agreement in April 2017. Although the Sub-Award Agreement expired by its terms on December 31, 2018, we expect to reach an agreement with CARB-X to extend the performance date out to June 30, 2019. The project can be terminated for convenience at any time.

Drug-Resistant Antibiotic Market

Physicians commonly prescribe antibiotics to treat patients with acute and chronic infectious diseases that are either presumed or known to be caused by bacteria. Inappropriate use of antibiotics and lack of new therapies has resulted in a rapid increase in bacterial infections that are resistant to multiple antibacterial agents. Global microbial resistance, including bacteria, viruses and fungi, now results in the death of at least 700,000 people each year, according to The Review on Antimicrobial Resistance, an analysis commissioned by the U.K. government in 2016. The report predicts that failing to develop effective treatments for drug-resistant bacteria by 2050 would lead to 10 million extra deaths a

year. Further, in a September 2013 report, the U.S. Centers for Disease Control and Prevention, or CDC, estimated that every year in the United States, more than two million people acquire serious infections that are resistant to one or more of the antibiotics designed to treat those infections, with at least 23,000 dying as a result, and many more dying from other conditions that are complicated by the occurrence of an antibiotic-resistant infection. These antibiotic-resistant infections add considerable and avoidable costs to the United States healthcare system. In the same September 2013 report, the CDC noted that the total economic cost of antibiotic-resistant infections to the United States economy has been estimated to be as high as $20 billion in excess direct healthcare costs. Over the last decade there has been an increase in antibiotics that target resistant Gram-positive bacteria, but there still remain limited therapeutic options for resistant Gram-negative infections. According to the CDC, among all of the bacterial resistance problems, Gram-negative pathogens are particularly worrisome because they are becoming resistant to nearly all drugs that would be considered for treatment, with the most serious Gram-negative infections being healthcare associated and the most common pathogens being Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter.

Antibiotics that treat bacterial infections can be classified as broad-spectrum or narrow-spectrum. Antibiotics that are active against a mixture of Gram-positive, Gram-negative and anaerobic bacteria are referred to as broad-spectrum. Antibiotics that are active only against a select subset of bacteria are referred to as narrow-spectrum. Because it usually takes from 24 to 72 hours from the time a specimen is received in the laboratory to definitively diagnose a particular bacterial infection, physicians may be required to prescribe antibiotics for serious infections without having identified the bacteria. As such, effective first-line treatment of serious infections, commonly referred to as empiric treatment, requires the use of broad-spectrum antibiotics with activity against a broad range of bacteria at least until the bacterial infection can be diagnosed.

Broad-spectrum antibiotics are used to treat major hospital infections such as cIAI. Based on an analysis from a variety of industry sources, we estimate that the number of patients treated with antibiotics in the United States and European Union annually includes approximately 4.6 million cIAI patients with each patient being treated for an average of 7.6 days for a combined estimated 40 million annual average days of treatment. Of these patients, we believe that approximately 40% of cIAI patients require a change in therapy and 50% of patients with cIAI are receiving combination therapy.

As such, at present, there is an acute need for new drugs to treat MDR Gram-negative bacteria. Currently approved products, such as meropenem, are becoming increasingly ineffective against Gram-negative bacteria due to increasing resistance, limiting patients' treatment options, particularly for patients with MDR infections. Few new therapeutic agents have been approved or are in clinical development.

Intra-abdominal infection is classified as uncomplicated or complicated based on the extent of the infection. cIAIs extend beyond the source organ into the peritoneal space (the space between the two membranes that separate the organs in the abdominal cavity from the abdominal wall) as a result of perforation or other damage to the gastrointestinal tract. cIAI diagnoses include intra-abdominal abscess, stomach or intestinal perforation, peritonitis, appendicitis, cholecystitis, or diverticulitis. Different bacterial pathogens are responsible for cIAI, including Gram-negative aerobic bacteria, Gram-positive bacteria, and anaerobic bacteria. Early detection, containment and appropriate antimicrobial treatment are essential to the successful treatment of IAI. This is even more critical with increasing rates of infections caused by drug-resistant bacteria, which limit the effectiveness of currently available antibiotics.

A nationwide electronic database looked at the prevalence of Gram-negative resistance from 2008-2015 in U.S. hospitals and it showed MDR rates continuing to increase. Out of the 3,158,349 isolates tested 5.3% were considered MDR pathogens. Five bacteria accounted for 92.7% of all MDR isolates: E coli (39.4%), P aeruginosa (29.4%), K pneumoniae (13.2%), A baumannii (5.4%) and Enterobacter spp (5.2%). The highest rate of MDR was associated with the onset in hospital setting (11.4%), followed by the admission period (6.6%), and the ambulatory setting (3.5%). In the database, 42.9% of A baumannii were MDR isolates. The rate of MDR A baumannii was highest in the inpatient setting (58.6% of isolates from all body sources), followed by admission setting (43.2%), and ambulatory setting (24.8%).

Legislative initiatives have been approved as part of the 21st Century Cures Act, including the Antibiotic Development to Advance Patient Treatment Act which would provide a pathway for approval of antibiotics in limited populations of patients with few or no suitable treatment options. Other legislation still pending include the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms, or DISARM, Act which would remove certain novel antibiotics used to treat serious bacterial infections from the diagnosis-related group and receive a drug specific reimbursement.

Limitations of Available Treatment Options

When confronted with a new patient suffering from a serious infection, such as cIAI, caused by an unknown pathogen, a physician may be required to quickly initiate first-line empiric antibiotic treatment to stabilize the patient prior to definitively diagnosing the particular bacterial infection. However, current antibiotics for first-line empiric treatment of serious bacterial infections suffer from significant limitations, including one or more of the following:

Insufficient Coverage Against MDR Bacteria. A physician cannot risk prescribing an inappropriate antibiotic when initially treating a patient for a serious infection due to well-documented increased rates of morbidity and mortality associated with ineffective empiric therapy or where the pathogen has not yet been definitively identified. Frequently used products, such as linezolid and daptomycin, are limited to Gram-positive bacteria and thus are rarely used as a first-line empiric monotherapy if broad bacterial coverage is required. Recently approved products are limited to specific Gram-negative bacteria and thus are rarely used as a first-line empiric monotherapy if broad bacterial coverage is required. In addition, other popular antibiotics that have been used as first-line empiric monotherapies, such as levofloxacin and piperacillin/tazobactam have seen their utility as first-line empiric monotherapies diminished as the number of bacterial strains resistant to these therapies has increased. In response, utilization of broader-spectrum, higher potency antibiotics, such as carbapenems, has increased. This has been accompanied by an increase in resistance to these agents such that the utility of the entire carbapenem class is now threatened.

Carbapenem Overuse and Increased Resistance. Carbapenems, such as meropenem and ertapenem, are considered the empiric drugs of choice for the treatment of a suspected or document cIAI caused by extended-spectrum beta-lactamase, or ESBL, producing Enterobacteriaceae. Finding alternatives to carbapenems for treatment of infections caused by ESBL-producing Enterobacteriaceae is an urgent medical need. Because ESBL producers are frequently also resistant to fluoroquinolones and piperacillin/tazobactam is less effective than a carbapenem, the options are scarce. The use of carbapenems is growing, which has led to increased resistance. In 2010, carbapenems were used for more than 8 million patient days of therapy, or DOTs, a number which doubled to 16 million DOTs by 2015. In parallel with this increased utilization, carbapenem-resistant enterobacteriaceae, or CRE, has been observed. Increased use of carbapenems is also associated with a higher rate of carbapenem-resistant Pseudomonas aeruginosa and Acinetobacter baumannii.

Penicillin Allergies. It is estimated that 10% of individuals in the United States report having a penicillin allergy which may limit empiric treatment options for serious infections including cIAI. Commonly prescribed alternatives to penicillin include fluoroquinolones, aztreonam or an aminoglycoside. However, these agents do not routinely provide adequate in vitro activity against the common Gram-negative pathogens which cause cIAI. Fluoroquinolones, which are the most commonly prescribed class in patients with penicillin allergies, have a black boxed warning due to serious side effects and are also associated with developing Clostridium difficile, or C. difficile, infection.

Poor Dose Optimization for Renally Impaired. With all beta-lactams, including carbapenems and piperacillin/tazobactam, it is necessary to adjust the dose for patients with renal impairment. This may cause problems with ensuring a patient is receiving an optimal dose when there are rapid changes in renal function associated with serious infections like cIAI. Xerava does not require dose adjustment for renal impairment, simplifying dosing in this setting.

Increased Risk of C. Difficile. Antibiotics are capable of disrupting the normal gut microflora, which can allow for C difficile to flourish and produce toxins. C. difficile is responsible for 20-30% of antibiotic-associated diarrhea cases and is the most common cause of infectious diarrhea in the healthcare setting. In general, a longer antibiotic duration and multiple antibiotics are two factors that increase the risk of antibiotic-associated C difficile diarrhea. Clindamycin carries the highest risk of C difficile infection, while fluoroquinolones, cephalosporins and carbapenems carry a fairly high risk,

Complicated and Expensive Multi-Drug Cocktails and Multi-Dose Regimens. Due to gaps in the spectrum of coverage of antibiotics, physicians are often confronted with the need to design complicated multi-drug cocktails for the first-line empiric treatment of patients with serious infections. The clinical situation is further complicated when each drug in the multi-drug cocktail has a different dosing regimen, such as three or four times a day, resulting in an added burden on the pharmacy and nursing staff, higher costs due to multiple drug administrations and an increased potential for medical errors or drug-drug interactions. We believe that, with the exception of Xerava, most of the antibiotics that are in development or have recently been approved by the FDA that are intended to cover a broad range of bacteria, including Gram-negative bacteria, or solely to address Gram-negative bacteria, are being developed or are approved for use in combination with one or more other antibiotics, and require the addition of a third drug such as metronidazole to address the presence of anaerobic bacteria. Multi-drug regimens may also be associated with toxicities not seen with the individual drugs, such as kidney injury, which has been reported when vancomycin and piperacillin/tazobactam are given together.

Safety and Tolerability Concerns. Concerns about antibiotic safety and tolerability are among the leading reasons why patients stop treatment and fail therapy. Antibiotics on the market have been associated with adverse effects such as myelosuppression, seizures, C. difficile colitis, nephrotoxicity and gastrointestinal disorders. Furthermore, allergies to beta-lactam antibiotics limit the utility of this class of antibiotics for up to 10% of patients.

Given these limitations, there is an unmet medical need for empiric antibiotic treatment that has the following characteristics:

- Potency and effectiveness against a broad range of bacteria, including MDR Gram-negative, Gram-positive, atypical and anaerobic bacteria;
- Offers an alternative to carbapenems;
- Capability of being used as a monotherapy in the majority of patients in the hospital with cIAI and other MDR infections;
- A convenient dosing regimen, such as once or twice-daily;
- A favorable safety and tolerability profile;
- No required dose adjustments for patients with impaired renal functions;

- No need for therapeutic drug monitoring for any patient group;
- Potent in vitro activity against C. difficile; and
- Ability to use in patients with penicillin and beta-lactam allergies

Based on our belief that Xerava and our pipeline candidates have, or potentially have, each of these characteristics, our goal is to develop Xerava and our pipeline candidates to be the drug of choice for first-line empiric treatment of a wide variety of serious and life-threatening infections.

Xerava (Eravacycline)

Overview

We developed Xerava using our proprietary chemistry technology, as an IV antibiotic for use as a first-line empiric monotherapy for the treatment of multidrug-resistant infections, including MDR Gram-negative infections such as those found in cIAI. On August 27, 2018, the FDA, approved Xerava for the treatment of cIAI in adults. On September 20, 2018, the EC, granted marketing authorization for Xerava for the treatment of cIAI in adults in all 28 countries of the EU, Norway, Iceland and Liechtenstein. Approval of Xerava in both the United States and in the EU was based on our IGNITE (Investigating Gram-Negative Infections Treated with Eravacycline) phase 3 program in cIAI.

To date, we have completed four phase 3 clinical trials with Xerava: IGNITE1 and IGNITE4, each a phase 3 clinical trial evaluating the safety and efficacy of Xerava with IV administration for the treatment of cIAI; IGNITE2, a phase 3 clinical trial evaluating the safety and efficacy of Xerava with IV-to-oral transition therapy for the treatment of complicated urinary tract infections, or cUTI, and IGNITE3, a phase 3 clinical trial evaluating the safety and efficacy of Xerava with IV administration for the treatment of cUTI.

In each of IGNITE1 and IGNITE4, Xerava met the primary endpoint of statistical non-inferiority compared to the control therapy for the trial and those trials formed the basis of the approval of Xerava by the FDA for the treatment of cIAI.

However, Xerava did not meet the primary endpoint of statistical non-inferiority in IGNITE2 compared to the control therapy for the trial and did not meet the co-primary endpoints of statistical non-inferiority in IGNITE3 compared to the control therapy for the trial. Given these results, we have ceased development of Xerava for the treatment of cUTI, including the oral formulation for Xerava for the treatment of cUTI.

Tetracycline antibiotics have been in clinical use for over 50 years and have a demonstrated record of safety and effectiveness. However, as with most classes of antibiotics, a high incidence of resistance among many bacteria has limited their effectiveness and resulted in tetracyclines being relegated to second- or third-line therapy several decades after their introduction. Chemists have generally been unable to synthesize new tetracyclines that could overcome bacterial resistance mechanisms. We have used our proprietary chemistry technology to create more than 3,000 new tetracycline derivatives that we believe could not be practically created with conventional methods. Many of these new derivatives, including Xerava, have been able to overcome bacterial resistance in in vitro studies.

Xerava is a novel, fully synthetic fluorocycline antibiotic. We selected Xerava for development from tetracycline derivatives that we generated using our proprietary chemistry technology. In designing Xerava, we inserted a fluorine atom into the tetracycline scaffold, which we call a fluorocycline, and modified the scaffold at another position. We believe that these modifications enable Xerava to not be subject to tetracycline-specific mechanisms of drug resistance. As a result, we believe that Xerava is active against MDR bacteria in ways that tetracyclines currently on the market or in development are not.

In in vitro studies, including a surveillance study published in December 2014 using over 4,000 patient bacterial isolates collected in New York City, Xerava has been highly active against emerging MDR pathogens like Acinetobacter baumannii as well as clinically important species of Enterobacteriaceae, including those isolates that produce ESBLs, or are resistant to the carbapenem class of antibiotics, and anaerobes, in comparison to commonly used antibiotics.

Data published in August 2016 demonstrated that in in vitro studies, Xerava retained potency against E. coli clinical isolates containing a plasmid expressing mcr-1, the gene associated with colistin resistance (ERV MIC_{90}=0.5 µg/mL; colistin MIC_{90}=16 µg/mL). The in vitro potency of Xerava was unaffected by inducible overexpression of the mcr-1 gene in an engineered laboratory E. coli strain.

Xerava has also demonstrated strong activity in vitro against Gram-positive pathogens, including both nosocomial and community-acquired methicillin susceptible or resistant Staphylococcus aureus strains, vancomycin susceptible or resistant Enterococcus faecium and Enterococcus faecalis, and penicillin-susceptible or resistant strains of Streptococcus pneumoniae. In in vitro studies of pathogens most prevalent in cIAI infections, Xerava consistently exhibited strong activity against enterococci and streptococci. One of the most frequently isolated anaerobic pathogens in cIAI, either as the sole pathogen or often in conjunction with another Gram-negative bacterium, is Bacteroides fragilis. In these studies, Xerava demonstrated activity against Bacteroides fragilis and a wide range of Gram-positive and Gram-negative anaerobes.

Key Differentiating Attributes of Xerava

We believe that the following key attributes of Xerava, observed in clinical trials and preclinical studies, differentiate Xerava from other antibiotics targeting multidrug-resistant infections, including MDR Gram-negative infections. We believe these attributes support Xerava as safe and effective treatment for cIAI and potentially for other serious and life-threatening infections for which we may develop Xerava.

- Offers a broad range of activity against a wide variety of MDR Gram-negative, Gram-positive and anaerobic bacteria. In our phase 2 and phase 3 clinical trials of the IV formulation of Xerava, Xerava demonstrated a high cure rate against a wide variety of MDR Gram-negative, Gram-positive and anaerobic bacteria. In addition, in in vitro studies, Xerava demonstrated potent antibacterial activity against Gram-negative bacteria, including ESBL-producing enterobacteriaceae; carbapenem-resistant Enterobacteriaceae (CRE); MCR-1 gene expressing bacteria; Acinetobacter baumannii, including carbapenem resistant Acinetobacter (CRAB); Gram-positive bacteria, including MRSA and vancomycin-resistant enterococcus, or VRE; and anaerobic pathogens. As a result, we believe that Xerava has the potential to be used as a first-line empiric monotherapy for the treatment of cIAI and potentially other serious and life-threatening infections.
- Lower probability of drug resistance. To date, in the clinical trials and preclinical studies of Xerava that we have conducted for the treatment of cIAI, we have seen little decrease in susceptibility that would suggest increased resistance to Xerava. We believe that, as a fluorocycline, Xerava will not be subject to tetracycline-specific mechanisms of drug resistance in certain MDR pathogens.
- Favorable safety and tolerability profile. Xerava has been evaluated in over 2,700 subjects in the phase 1, phase 2 and phase 3 clinical trials that we have conducted through February 2018. In these trials, Xerava has demonstrated a favorable safety and tolerability profile. In our phase 2 and phase 3 clinical trials of Xerava in patients with cIAI, no patients suffered any drug-related serious adverse events, and safety and tolerability were comparable to the respective control therapies for the trials. In the phase 3 clinical trials of Xerava in patients with cUTI, safety and tolerability were comparable to the respective control therapies for these trials. In addition, in these phase 2 and phase 3 clinical trials, the rate at which gastrointestinal adverse events such as nausea and emesis occurred in the Xerava arms was low. Since Xerava is not a beta-lactam, it also offers an alternative treatment for patients with allergies to this commonly used antibiotic class.
- Lower risk of Clostridium difficile colitis. Xerava, like other tetracycline class antibiotics, has shown activity against C. difficile in in vitro studies and, therefore, may be associated with a lower risk of C. difficile colitis compared with other broad-spectrum antibiotics.
- Convenient dosing regimen. In our clinical trials to date, we have dosed Xerava once or twice a day as a monotherapy. We believe that Xerava will be able to be administered as a first-line empiric monotherapy with twice-daily dosing, avoiding the need for complicated dosing regimens typical of multi-drug cocktails and the increased risk of negative drug-drug interactions inherent to multi-drug cocktails.
- No dosage adjustment required for impaired renal function. Unlike other classes of antibiotics, such as beta-lactams, Xerava does not require dosage adjustment in patients with impaired renal function. In addition to convenience, this ensures that patients with rapidly fluctuating renal function do not have high drug levels, which could lead to toxicity, or low drug levels which could result in loss of efficacy.

Clinical Experience

We have studied IV and oral formulations of Xerava in over 2,700 subjects in 21 clinical trials completed from October 2009 to February 2018.

Phase 3 Clinical Program in cIAI

We designed our IGNITE phase 3 program for Xerava in cIAI to enable us to position Xerava as a first-line empiric monotherapy for the treatment of cIAI due to Xerava's broad-range of coverage against resistant and MDR infections, including MDR Gram-negative infections.

Our initial phase 3 clinical trial of Xerava for the treatment of patients with cIAI was our IGNITE1 trial. In December 2014, we announced that Xerava met the primary endpoint of statistical non-inferiority compared to ertapenem in IGNITE1 for the treatment of cIAI. In July 2017, we announced that Xerava met the primary endpoint of statistical non-inferiority compared to meropenem in IGNITE4 for the treatment of cIAI.

IGNITE1

Eravacycline Phase 3 IGNITE1 Study Design

We designed IGNITE1 as a non-inferiority study. Under FDA guidance, the primary endpoint of the trial was clinical response at the test-of-cure, or TOC, visit in the microbiological intent-to-treat, or micro-ITT, population which consisted of all randomized patients in the trial who had baseline bacterial pathogens that cause cIAI and against which Xerava has antibacterial activity. Under EMA guidance, the primary endpoint of the trial was clinical response at the TOC visit in the modified intent-to-treat, or MITT, population which consisted of all patients who received at least one dose of study drug, and in the clinically evaluable, or CE, patient population, which consisted of all randomized patients in the trial who meet key inclusion/exclusion criteria and follow other important components of the trial. We designed the trial to be consistent with the FDA's cIAI guidance, in which the FDA suggested that the primary efficacy endpoint for a trial of cIAI should be complete resolution of baseline signs and symptoms attributable to cIAI in the micro-ITT patient population 28 days after randomization and the absence of clinical failure including death and unplanned surgical procedures through the period ending 28 days following randomization.

In December 2014, we announced top-line data from IGNITE1. In the trial, Xerava met the primary endpoint of statistical non-inferiority of clinical response at the TOC visit, under the guidance set by the FDA and the EMA. The primary analysis under the FDA guidance was conducted using a 10% non-inferiority margin in the micro-ITT population. In the micro-ITT population, the lower and upper bounds of the 95% confidence interval were -7.1% and 5.5%, respectively. Under the EMA guidance, the primary analysis was conducted using a 12.5% non-inferiority margin in the CE and MITT patient populations. In the CE population, the lower and upper bounds of the 95% confidence interval were -6.3% and 2.8%, respectively, and the lower and upper bounds of the 99% confidence interval were -7.9% and 4.4%, respectively. In the MITT population, the lower and upper bounds of the 95% confidence interval were -7.4% and 3.8%, respectively, and the lower and upper bounds of the 99% confidence interval were -9.2% and 5.6%, respectively. The most commonly reported drug-related adverse events for Xerava were gastrointestinal, including nausea (3.3%) and emesis (2.2%). This adverse event profile for Xerava was consistent with that seen in the phase 2 clinical trial of Xerava in cIAI. The spectrum of pathogens in this trial was similar to that seen in other pivotal trials of antibiotics in this patient population. The most common Gram-negative pathogens in the trial included Escherichia coli, Klebsiella pneumonia, Pseudomonas and Bacteroides.

8

IGNITE4

Eravacycline Phase 3 IGNITE4 Study Design

We designed IGNITE4 as a non-inferiority study. Under FDA guidance, the primary endpoint of the trial was clinical response at the TOC visit in the micro-ITT population, which consisted of randomized patients in the trial who had baseline bacterial pathogens that cause cIAI and against which Xerava has antibacterial activity. Under EMA guidance, the primary endpoint of the trial was clinical response at the TOC visit in the MITT population, which consisted of patients in the trial who received at least one dose of study drug, and in the CE patient population, which consisted of patients in the trial who met key inclusion/exclusion criteria and followed other important components of the trial. Secondary endpoints included clinical response at the end-of-treatment, TOC and follow-up visits in the intent-to-treat population, the CE population, the micro-ITT population and the microbiologically evaluable, or ME, population. The ME population consisted of all micro-ITT patients who met key inclusion/exclusion criteria and followed other important components of the trial. In the trial, we also studied microbiologic response at the end-of-treatment and TOC visits in the micro-ITT and ME populations, the safety and tolerability of Xerava in the safety population and pharmacokinetic parameters after Xerava administration.

On July 25, 2017, we announced top-line data from IGNITE4. In the trial, Xerava met the primary endpoint of statistical non-inferiority of clinical response at the TOC visit, under the guidance set by the FDA and the EMA. The primary efficacy analysis under the FDA guidance was conducted using a 12.5% non-inferiority margin in the micro-ITT population. Clinical cure rates in the micro-ITT population were 90.8% and 91.2% for Xerava (n=195) and meropenem (n=205), respectively (95% CI: -6.3%,5.3%). Under the EMA guidance, the primary analysis was conducted using a 12.5% non-inferiority margin of the MITT and CE patient populations. Clinical cure rates in the MITT population were 92.4% and 91.6% for Xerava (n=250) and meropenem (n=249), respectively (95% CI: -4.1%,5.8%). Clinical cure rates in the CE population were 96.9% and 96.1% for Xerava (n=225) and meropenem (n=231), respectively (95% CI: -2.9%,4.5%). The secondary analyses were consistent with, and supportive of, the primary outcome. The most commonly reported drug-related adverse events for Xerava were gastrointestinal, including nausea (2.4%) and emesis (1.6%). This adverse event profile for Xerava was consistent with that seen in the phase 2 clinical trial of Xerava in cIAI. The spectrum of pathogens in this trial was similar to that seen in other pivotal trials of antibiotics in this patient population. The most common Gram-negative pathogens in the trial included Escherichia coli, Klebsiella pneumonia, Pseudomonas and Bacteroides.

TP-6076

TP-6076, a fully-synthetic fluorocycline derivative, is designed to target unmet medical needs, including MDR Gram-negative bacteria such as Acinetobacter baumannii. We created TP-6076 using our proprietary technology. TP-6076 has demonstrated potent activity in vitro against carbapenem-resistant Acinetobacter Baumanii (CRAB) as well as efficacy in animal models of CRAB pneumonia. In June 2017, we announced positive results from a phase 1 randomized, placebo-controlled, double-blind, single-ascending dose study evaluating the safety, tolerability and pharmacokinetics of IV TP-6076. In the study, TP-6076 was well tolerated, and there were no serious or severe adverse events, or discontinuations due to an adverse event. In October 2018, we announced results of a phase 1 study of the safety, tolerability, and pharmacokinetics of multiple doses of IV TP-6076 in healthy volunteers. In this study, multiple doses of TP-6076 were generally well tolerated with no serious or severe adverse events and no clinically significant findings in any laboratory assessments, vital signs, ECGs, or physical examinations. We are currently conducting a Phase 1 study to assess the bronchopulmonary disposition, pharmacokinetics, and safety of TP-6076 in healthy volunteers.

Funding for TP-6076 is partially covered by an award from CARB-X. In March 2017, CARB-X selected us to receive up to $4.0 million in research funding over eighteen months for TP-6076. In connection with this funding, we entered into a cost reimbursement Sub-Award Agreement or “Sub-Award Agreement”, with the Trustees of Boston University, the administrator of the program. We began recognizing revenue from the Sub-Award Agreement in April 2017. During the year ended December 31, 2018, we recognized revenue of $2.0 million under this Sub-Award Agreement. Although this Sub-Award Agreement expired by its terms on December 31, 2018, we expect to reach an agreement with CARB-X to extend the performance date out to June 30, 2019. This Sub-Award Agreement can be terminated for convenience at any time, subject to 30 days prior written notice.

TP-271

TP-271 is a fully-synthetic, broad-spectrum fluorocycline developed for the treatment of respiratory diseases caused by bacterial biothreat pathogens under funding provided by NIAID in collaboration with CUBRC.

We created TP-271 using our proprietary chemistry technology. In doing so, we made modifications to the tetracycline scaffold that were designed to improve potency and effectiveness against a broader spectrum of bacteria as compared to tetracycline and doxycycline, which are currently used for the treatment of pneumonia and other respiratory ailments.

In our development program for TP-271, we have conducted a number of in vitro, toxicology and animal studies to evaluate the efficacy of TP-271 against biothreat pathogens. TP-271 has performed as well as, or better than, standard-of-care comparators in studies in murine respiratory infection models challenged with public health pathogens. In susceptibility studies, TP-271 also demonstrated broad-spectrum activity against NIAID Category A and B public health bacterial pathogens including Francisella tularensis, Yersinia pestis, Burkholderia mallei, Burkholderia pseudomallei, Bacillus anthracis, and NIAID Category C public health bacterial pathogens (in vitro and in vivo) that are associated with CABP, including Streptococcus pneumoniae, including MDR pneumococci, Staphylococcus aureus (methicillin-susceptible and methicillin-resistant), Haemophilus influenzae, Moraxella catarrhalis and Legionella pneumophila, including strains that are tetracycline-resistant.

In June 2017, we announced positive results from a phase 1 single-ascending dose clinical trial of the IV formulation of TP-271 in healthy volunteers. In the study, TP-271 was well-tolerated at single doses that resulted in high plasma exposures. There were no clinically significant changes in lab values, ECG parameters, or physical exam findings. There were no serious or severe adverse events, or discontinuations due to an adverse event during the study. We also completed a single-ascending dose trial for the oral formulation of TP-271, and multiple-ascending dose trials for the

IV and oral formulations of TP-271. We expect to report results of these studies at a future scientific meeting. In February 2017, we received Qualified Infectious Disease Product and Fast Track designations from the FDA for TP-271.

For explanation of the funding for TP-271 and for further discussion of our contract and grant revenue agreements see Note 3, Significant Agreements and Contracts to the consolidated financial statements.

TP-2846

TP-2846 is a fully-synthetic tetracycline that we are developing for the treatment of AML. We have recently initiated pre-clinical toxicology studies in this program. In pre-clinical studies, TP-2846 demonstrated significant activity against leukemia cell lines, both in vitro and in vivo.

Sales and Marketing

We have established a targeted commercial organization in the United States to support the launch of Xerava. As of March 1, 2019, we had approximately 40 sales representatives, three strategic market access executives and approximately 10 medical affairs personnel supporting Xerava. Our sales force has on average 25 years of hospital sales experience and launching antibiotics. We also have tenured and focused marketing and sales operations teams located at our headquarters in Watertown, Massachusetts.

Our commercialization strategy is to develop our product candidates into leading therapies that will be available worldwide for the treatment of serious MDR infections. We have retained worldwide commercial rights to all of our product candidates other than Xerava in China and other Asian territories. We exclusively licensed our commercial rights to Xerava in China and other Asian territories to Everest Medicines Limited in February 2018. In the future we may enter into additional regional licensing transactions similar to the Everest license agreement. We intend to retain control over the commercial execution of Xerava and any product candidate in the United States and in certain countries in the EU.

Manufacturing and Supply

We do not own or operate manufacturing facilities for the production of Xerava or any of our product candidates, nor do we have plans to develop our own manufacturing operations in the foreseeable future. Xerava and our product candidates are organic compounds of low molecular weight, commonly referred to as small molecules. They are manufactured in a fully synthetic process from readily available starting materials.

We currently rely on a limited number of third-party contract manufacturers for all of our required raw materials, drug substance and finished product for our preclinical research and clinical trials. We do not have long-term agreements with any of these third parties other than with respect to our agreements with third-party contract manufacturers for the commercial production of Xerava. We currently employ internal resources to manage our third-party manufacturing relationships.

Patheon UK Limited Master Manufacturing Services Agreement

In June 2017, we and Patheon UK Limited and certain of its affiliates, or Patheon, entered into a master manufacturing services agreement, or the Patheon agreement. Under the Patheon agreement, we are responsible for supplying the active pharmaceutical ingredient for Xerava to Patheon, and Patheon is responsible for manufacturing Xerava, conducting quality control, quality assurance, analytical testing and stability testing and packaging. We entered into two related product agreements pursuant to the Patheon agreement that govern the terms and conditions of Patheon’s manufacture of commercial supplies of Xerava at Patheon’s Greenville, North Carolina and Ferentino, Italy manufacturing sites. Each product agreement is governed by the terms of the Patheon agreement, unless expressly modified in such product agreement. Pursuant to the Patheon agreement, we have agreed to order from Patheon at least a certain percentage of our annual commercial requirements for Xerava in the United States and European Union each year for the term of the Patheon agreement.

Under the Patheon agreement, we will submit to Patheon by a date in June of a calendar year the forecast for the following two years that sets forth the total quantity of Xerava commercial supply that we expect to order from Patheon. Patheon has no obligation to manufacture the Xerava commercial supply in accordance with any forecast which is increased by a certain percentage above the previously forecast amount.

The Patheon agreement has an initial term ending December 31, 2022, and will automatically renew after the initial term for successive terms of two years each, unless either party gives notice of its intention to terminate at least 18

months prior to the end of the then current term. We may terminate a product agreement upon 30 days' prior written notice if any governmental agency takes any action that prevents us from importing, exporting, purchasing or selling Xerava. Either party may terminate the Patheon agreement or a product agreement (a) upon written notice if the other party has failed to remedy a material breach under the Patheon agreement or a product agreement within a specified time following receipt of written notice of such breach, and (b) immediately upon written notice to the other party in the event that the other party is declared insolvent or bankrupt, a voluntary petition of bankruptcy is filed in any court by such other party or the Pantheon agreement or a product agreement is assigned by such other party for the benefit of creditors. Patheon may terminate the Patheon agreement or a product agreement upon six months written notice if we assign the Patheon agreement to an assignee that, in the opinion of Patheon acting reasonably, is (i) not a creditworthy substitute for us or (ii) a competitor of Patheon.

The Patheon agreement contains, among other provisions, customary representations and warranties by the parties, a grant to Patheon of certain limited license rights to our intellectual property in connection with Patheon's performance of the services under the Patheon agreement, certain indemnification rights in favor of both parties, limitations of liability and customary confidentiality provisions.

Finorga SAS Commercial Supply Agreement

In October 2017, we and Finorga SAS, or Novasep entered into a Commercial Supply Agreement, or the Novasep agreement. Under the Novasep agreement, Novasep will, pursuant to accepted purchase orders entered into under the Novasep agreement, manufacture for commercial supply the active pharmaceutical ingredient, or API, for Xerava for us.

Under the Novasep agreement, we will submit to Novasep on a periodic basis on or before the first business day of each calendar quarter a rolling forecast for a certain time period that sets forth the total quantity of the API for Xerava for commercial supply that we either have ordered, desire to order or expect to order from Novasep. A certain time period of each such forecast is binding on us and constitutes a “firm order”. The remainder of each forecast will be for planning purposes only and will not be binding. Novasep has no obligation to manufacture the API for Xerava in accordance with any forecast that is not the subject of a firm order and which is increased by a certain percentage above the previously forecast amount.

The Novasep agreement has an initial term ending October 16, 2022, and will automatically renew after the initial term, unless either party gives notice of its intention to terminate at least 18 months prior to the end of the then current term. We may terminate the Novasep agreement upon 30 days’ prior written notice (a) if any regulatory authority takes any action, or raises any objection, that prevents us from importing, exporting, purchasing or selling the API for Xerava, or (b) in the event that Novasep experiences a force majeure event. Either party may terminate the Novasep agreement (a) upon written notice if the other party has failed to remedy a material breach under the Novasep agreement within a specified time following receipt of written notice of such breach, and (b) immediately upon written notice to the other party in the event the other party makes a general assignment for the benefit of its creditors, or proceedings of a case are commenced in any court of competent jurisdiction by or against the other party seeking (i) such party’s reorganization, liquidation, dissolution, arrangement or winding up, or the composition or readjustment of its debts, (ii) the appointment of a receiver or trustee for or over such party’s property, or (iii) similar relief in respect of such party under any law relating to bankruptcy, insolvency, reorganization, winding up or composition or adjustment of debt, and such proceedings shall continue undismissed, or an order with respect to the foregoing shall be entered and continue unstayed, for a period of more than 60 days.

The Novasep agreement contains, among other provisions, customary representations and warranties by the parties, a grant to Novasep of certain limited license rights to the Company’s intellectual property in connection with Novasep’s performance of the services under the Novasep agreement, certain indemnification rights in favor of both parties, limitations of liability and customary confidentiality provisions.

Intellectual Property

We strive to protect the proprietary technology that we believe is important to our business, including seeking and maintaining patents intended to cover our product candidates and compositions, their methods of use and processes for their manufacture and any other inventions that are commercially important to the development of our business. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will significantly depend on our ability to obtain and maintain patent and other proprietary protection for commercially important technology and inventions and know-how related to our business, defend and enforce our patents, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how and continuing technological innovation to develop and maintain our proprietary position.

As of February 13, 2019, we owned 11 U.S. patents, 65 foreign patents, nine pending U.S. patent applications, two pending applications filed under the Patent Cooperation Treaty, or PCT, and 50 pending foreign patent applications in Europe and 20 other jurisdictions. The PCT is an international patent law treaty that provides a unified procedure for filing a single initial patent application for an invention simultaneously in each of the member states. Although a PCT application is not itself examined and cannot issue as a patent, it allows the applicant to seek protection in any of the member states through national-phase applications. In addition, we have exclusively licensed from Harvard University rights under 12 U.S. patents, 34 foreign patents, one pending U.S. patent application and six pending foreign patent applications in Europe and ten other jurisdictions. Certain of our patents and patent applications are directed to the composition of matter and/or use of Xerava and patents have granted, or applications are pending in the United States, Europe, Japan and other countries.

Tetraphase-Owned Intellectual Property Relating to Xerava and Other Compounds Under Development

We have patent applications directed to the composition of matter and/or use of Xerava and other fluorocyclines pending in the United States and other countries. In addition, patents specific to the composition of matter, pharmaceutical compositions and/or use of Xerava have been granted in the United States, Europe, Australia, China, Colombia, India, Japan, Korea, Mexico, New Zealand, Hong Kong, Taiwan, Israel and Singapore. The granted patents have an expiration date of August 7, 2029, and any patents that may issue from the pending applications will also have an expiration date of August 7, 2029, absent any term extensions or adjustments that may be available. The term of one of the United States patents has received 508 days of patent term adjustment under the America Invents Act.

We have a pending PCT application directed to crystalline forms of Xerava. Any patents that may issue based on the pending PCT Application will have an expiration date no earlier than 2037.

We have also filed patent applications directed to the composition of matter and use of various derivatives of tetracycline and pentacycline (a tetracycline scaffold extended to five rings) under the PCT and in the United States, Europe and other foreign countries. Any patents that might issue from these pending applications will have an expiration date no earlier than 2030, with some expiration dates as late as 2038.

Exclusively Licensed Intellectual Property Relating to Our Proprietary Chemistry Technology

The patents and patent applications that we exclusively license from Harvard provide patent protection for the proprietary chemistry technology used in our fully synthetic process to make Xerava and other tetracycline derivatives. The key intermediates that enable our fully synthetic process are commonly referred to as enone intermediates. The licensed patents and patent applications are directed towards the composition of matter of enone intermediates and compounds used to make the enone intermediates, referred to as key precursors, as well as synthetic routes to those enone intermediates, precursors and our tetracycline derivatives under development.

Composition of matter for the enone intermediates and precursors used in preparing the enone intermediates, and methods of making the precursors and enone intermediates are covered by the U.S. patents we license from Harvard, which will expire no earlier than 2025, not taking into consideration patent term adjustment. Corresponding patent applications have been filed in foreign jurisdictions and any patents that have issued and might issue from these applications also expire or will expire no earlier than 2025.

Exclusively Licensed Intellectual Property Relating to Pentacycline and Tetracycline Derivatives

Our license from Harvard also includes patent applications directed to the composition of matter and use of other novel tetracycline or pentacycline derivatives. These applications are pending in the United States, Europe and other countries. Any patents that might issue from these pending applications will have an expiration date no earlier than 2027.

Patent Term and Patent Term Extensions

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent’s term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in examining and granting a patent or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug, biological product or medical device approved pursuant to a pre-market approval may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements

are met. The length of the patent term extension is related to the length of time the drug is under regulatory review while the patent is in force. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration date set for the patent. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent applicable to each regulatory review period may be granted an extension and only those claims reading on the approved drug are extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug.

Trademark Applications Relating to the Company Name and Logo

As of February 13, 2019, we owned eight intent-to-use trademark applications pending before the United States Patent and Trademark Office relating to the Company Name, the Company Logo, combinations thereof, drug names and design marks relating to Xerava.

Trade Secrets

We rely, in some circumstances, on trade secrets to protect our unpatented technology. However, trade secrets can be difficult to protect. We seek to protect our trade secrets and proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, scientific advisors and contractors. 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. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached. We may not have adequate remedies for any breach and could lose our trade secrets through such a breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting trade secrets, know-how and inventions.

Third-Party License Agreements

On August 3, 2006, we entered into a license agreement with The President and Fellows of Harvard College, under which Harvard granted us an exclusive worldwide license under specified Harvard patent rights to develop and commercialize tetracycline-based products such as Xerava. Under the license agreement, we also have the right to expand the patent rights subject to the license to include improvement patents that may be owned by Harvard in the future and that meet specified criteria by paying to Harvard an additional license issuance fee in an amount to be agreed between Harvard and us. We also have a right of negotiation to expand the license to include additional patents relating to tetracycline chemistry within a specified category that may be owned by Harvard in the future, including patents covering inventions made by Andrew Myers, Ph.D., our scientific founder, under his consulting agreement with us. Since entering into the license agreement, we have entered into amendments to the license agreement pursuant to which we expanded the patent rights subject to the license in accordance with these rights. Under the license agreement, we are obligated to satisfy diligence requirements, including using commercially reasonable efforts to develop and commercialize licensed compounds and to implement a specified development plan, meeting specified development milestones and providing an update on progress on an annual basis. Our license grant from Harvard is subject to academic rights retained by Harvard and United States government rights and obligations that are customary in patent license agreements with universities in the United States.

In consideration for the rights granted to us by Harvard under the license agreement, as of December 31, 2018, we have paid Harvard an aggregate of $15.8 million in upfront license fees, sublicense fees and development milestone payments and issued 31,379 shares of our common stock to Harvard. We have also agreed to make payments to Harvard upon the achievement of specified future development and regulatory milestones totaling up to $15.1 million for each licensed product candidate ($12.6 million of which has already been paid with respect to Xerava), and to pay tiered royalties in the single digits based on annual worldwide net sales, if any, of licensed products by us, our affiliates and sublicensees in certain circumstances. We are also obligated to pay Harvard a specified share of non-royalty sublicensing and other revenues that we receive from sublicensees for the grant of sublicenses under the license in certain circumstances, and to reimburse Harvard for specified patent prosecution and maintenance costs.

The Harvard license agreement expires on a licensed product-by-licensed product and country-by-country basis upon the expiration of the last-to-expire patent covering the applicable product in the applicable country that is included in the license. Harvard may terminate the license agreement based on our uncured material breach or insolvency or bankruptcy. We have the right to terminate the license agreement for any or no reason at any time on sixty (60) days prior written notice to Harvard.

Government Contracts

Xerava

We received funding for Xerava under an award from BARDA. In January 2012, BARDA awarded to CUBRC a five-year contract that provided a total of up to $67.3 million in funding. The BARDA Contract contemplates that CUBRC will collaborate with us on the development, manufacturing and clinical evaluation of a novel tetracycline antibiotic with potential as an empiric countermeasure for respiratory diseases caused by biothreat and antibiotic-resistant public health pathogens, including Francisella tularensis, which causes tularemia, Yersinia pestis, which causes plague, and Bacillus anthracis, which causes anthrax disease, as well as bacterial pathogens associated with moderate-to-severe CABP and other serious hospital infections. The BARDA Contract also provided funding for certain activities in the development of Xerava to treat certain infections caused by life-threatening multidrug-resistant bacteria. In connection with the BARDA Contract, in February 2012, we entered into a cost-plus-fixed-fee subcontract with CUBRC under which we can receive up to $41.8 million to fund specific work performed by us related to Xerava. The terms of the subcontract expire on March 30, 2019.

We collaborated with CUBRC in seeking government funding of this development program because we did not have any expertise in bidding for, or the administration and management of, government-funded contracts. Because CUBRC had the expertise to manage and administer awards issued by government funding agencies, we agreed with CUBRC that CUBRC would serve as the prime contractor under the BARDA Contract, primarily carrying out a program management and administrative role with additional responsibility for the management of certain preclinical studies. We serve as lead technical experts on all aspects of the BARDA Contract and serve as a subcontractor of CUBRC responsible for management of chemistry, manufacturing and control activities and clinical studies. The flow of funds under this arrangement follows the respective activities being conducted by us and by CUBRC, with funds being paid to us under our subcontract with CUBRC reflecting payment for our activities.

We have agreed upon a research plan with CUBRC detailing the activities to be conducted by CUBRC and by us. In addition to our obligations to conduct the activities provided for by the research plan, we are also obligated under the CUBRC subcontract to satisfy various federal reporting requirements, extending to technical reporting with respect to our activities, reporting with respect to intellectual property and financial reporting.

Payments under our subcontract with CUBRC are made in installments as activities are conducted in accordance with the research plan. Payments are based on direct and indirect costs incurred plus fixed fees, where applicable.

Under the subcontract, CUBRC's use of our Xerava data is expressly limited to purposes of performing CUBRC's obligations under the BARDA Contract, and CUBRC and its other subcontractors must assign to us, subject to government rights, all intellectual property rights relating to our compounds and related data that arise from the project. Under standard government contracting terms, the government receives only limited rights for government use of certain of our pre-existing data and certain data produced with non-federal funding, to the extent such data are required for delivery to BARDA under the project. The government receives unlimited rights to use and disclose new data first produced under the project with BARDA funding, and the government is entitled to at least a nonexclusive, worldwide, royalty-free license to practice or have practiced any patent on an invention that is conceived or first reduced to practice under the project.

BARDA is entitled to terminate the project for convenience at any time and is not obligated to provide continued funding beyond current-year amounts from Congressionally approved annual appropriations, and CUBRC has a right to terminate its subcontract with us only to the extent that BARDA first cancels the corresponding portions of CUBRC's prime contract.

We retain a right to terminate CUBRC's rights to use Xerava. Permissible grounds for such termination of CUBRC's rights include but are not limited to the sale of our assets relating to the project, an acquisition of us or our granting an exclusive or partially exclusive license to use Xerava to a licensee that declines to continue CUBRC's license rights. In such an event, the subcontract may be terminated upon CUBRC's negotiation of a corresponding termination of CUBRC's obligations to BARDA.

TP-6076

Our program to develop TP-6076 is partially covered by an award from CARB-X. In March 2017, CARB-X selected the Company to receive up to $4.0 million in research funding over eighteen months for TP-6076. In connection with this funding, the Company entered into a cost reimbursement Sub-Award Agreement with the Trustees of Boston University, the administrator of the program. Although this Sub-Award Agreement expired by its terms on December 31, 2018, we expect to reach an agreement with CARB-X to extend the performance date out to June 30, 2019. This Sub-Award Agreement can be terminated for convenience at any time, subject to 30 days prior written notice.

TP-271

Our program to develop TP-271 is funded by NIAID through the NIAID Grant, a grant awarded in July 2011 that provided up to approximately $2.9 million in funding, and the NIAID Contract, a separate agreement that provides up to $35.8 million in funding that NIAID awarded to CUBRC in October 2011. The NIAID Contract and the NIAID Grant contemplate that CUBRC will collaborate with us on the development, manufacturing and clinical evaluation of a novel broad-spectrum tetracycline antibiotic for respiratory diseases caused by biothreat and antibiotic-resistant public health pathogens, including Francisella tularensis, Yersinia pestis and Bacillus anthracis, as well as bacterial pathogens associated with CABP.

In connection with the NIAID Contract, in October 2011, we entered into a subcontract with CUBRC under which we may receive funding of up to approximately $16.9 million, reflecting the portion of the NIAID Contract funding that may be paid to us for our activities. The term of the NIAID subcontract now runs through March 31, 2019. In connection with the NIAID Grant, in November 2011, CUBRC awarded us a subaward of approximately $0.9 million, reflecting the portion of the NIAID Grant funding that may be paid to us for our activities. The term of the sub-award under the NIAID grant expired in May 2017.

We collaborated with CUBRC in seeking government funding of this development program because we did not have any expertise in bidding for, or the administration and management of, government-funded contracts. Because CUBRC had the expertise to manage and administer awards issued by government funding agencies, we agreed with CUBRC that CUBRC would serve as the prime contractor under the NIAID Contract, primarily carrying out a program management and administrative role with additional responsibility for the management of certain preclinical studies. We serve as lead technical experts on all aspects of the NIAID Contract and serve as a subcontractor of CUBRC responsible for management of chemistry, manufacturing and control activities and clinical studies. The flow of funds under this arrangement follows the respective activities being conducted by us and by CUBRC, with funds being paid to us under our subcontract with, and subaward from, CUBRC reflecting payment for our activities.

We have agreed upon a research plan with CUBRC detailing the activities to be conducted by CUBRC and by us. In addition to our obligations to conduct the activities provided for by the research plan, we are also obligated under the CUBRC subcontract to satisfy various federal reporting requirements, extending to technical reporting with respect to our activities, reporting with respect to intellectual property and financial reporting.

Payments under our subcontract with CUBRC are made in installments as activities are conducted in accordance with the research plan. Payments are based on direct and indirect costs incurred plus fixed fees, where applicable.

Under the subcontract, CUBRC's use and disclosure of our proprietary data pertaining to the project are expressly subject to a separate confidentiality agreement between CUBRC and us. CUBRC and its other subcontractors or sub-awardees must assign to us, subject to government rights, all intellectual property rights relating to our compounds and related data that arise from the project. Under standard government contracting terms and grant conditions, the government is entitled to at least a nonexclusive, worldwide, royalty-free license to practice or have practiced any patent on an invention that is conceived or first reduced to practice under the project.

NIAID is entitled to terminate the NIAID Contract for convenience at any time and is not obligated to provide continued funding beyond March 31, 2019 and CUBRC has a right to terminate its subcontract with, or subaward to, us only to the extent that NIAID first cancels the corresponding portions of CUBRC's prime contract or award.

We retain rights to terminate the subcontract if CUBRC breaches the subcontract, subject in certain cases to CUBRC's failure to cure such breach, or by written notice to CUBRC, effective upon CUBRC's negotiation of a corresponding termination of CUBRC's obligations to NIAID.

Collaborations

In February 2018, we entered into a license agreement, which we call the Everest license agreement, with Everest Medicines Limited, or Everest Medicines, whereby we granted Everest Medicines an exclusive license to develop and commercialize eravacycline, for the treatment of cIAI and other indications, in mainland China, Taiwan, Hong Kong, Macau, South Korea and Singapore, or the territory.

Under the terms of the Everest license agreement, we received from Everest Medicines an upfront cash payment of $7.0 million and are entitled to receive up to an aggregate of $16.5 million in clinical development and regulatory milestone payments and up to $20.0 million provided that certain sales thresholds are met. To date, we have received $2.5 million from Everest in clinical development and regulatory milestones. There can be no guarantee that any such milestones or sales thresholds will in fact be met. We are obligated to make certain payments to Harvard based on amounts received from Everest Medicines under the Everest license agreement pursuant to the existing license agreement by and between Harvard and us.

We will also be entitled to receive double-digit tiered royalties on sales in the territory, if any, of products containing eravacycline. Royalties are payable with respect to each jurisdiction in the territory until the latest to occur of: (i) the last-to-expire of specified patent rights in such jurisdiction in the territory; (ii) expiration of marketing or regulatory exclusivity in such jurisdiction in the territory; or (iii) ten (10) years after the first commercial sale of a product in such jurisdiction in the territory. In addition, royalties payable under the Everest license agreement will be subject to reduction on account of generic competition and after patent expiry in a jurisdiction if required by applicable law, with any such reductions capped at certain percentages of the amounts otherwise payable during the applicable royalty payment period.

Under the terms and conditions of the Everest license agreement, Everest Medicines will be solely responsible for the development and commercialization of licensed products in the territory.

If either we or Everest Medicines materially breaches the Everest license agreement and does not cure such breach within 90 days (or fewer days in certain cases), the non-breaching party may terminate the Everest license agreement in its entirety. However, if the breach relates only to any jurisdiction other than mainland China, the non-breaching party may only terminate the Everest license agreement with respect to such jurisdiction. Either party may also terminate the Everest license agreement, effective immediately upon written notice, if the other party files for bankruptcy, is dissolved or has a receiver appointed for substantially all of its property. We may terminate the Everest license agreement if Everest Medicines, its affiliates or its sublicensees challenges the validity or enforceability of any of our patents covering any of the licensed compounds or products. In certain circumstances, if we materially breach the Everest license agreement Everest Medicines may reduce royalties owed to us in lieu of a termination. Moreover, if we materially breach the Everest license agreement and Everest Medicines terminates the Everest license agreement with respect to any jurisdiction and we then commercializes a licensed product in that jurisdiction, we will pay to Everest Medicines a low, single digit royalty on such sales of the licensed product in such jurisdiction for a minimum of five years after such termination.

Competition

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Our potential competitors include large pharmaceutical and biotechnology companies, specialty pharmaceutical companies and generic drug companies. Many of our potential competitors have greater financial, technical and human resources than we do, as well as greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our potential competitors may be more successful than us in achieving widespread market acceptance. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available. Finally, the development of new treatment methods for the diseases we are targeting could render our product candidates less competitive or obsolete.

We believe the key competitive factors that may affect the commercial success of Xerava for the treatment of cIAI are; efficacy, coverage of drug-resistant strains of bacteria, safety and tolerability profile, convenience of dosing, price, and the availability of reimbursement from governmental and other third-party payers. Outside factors that may affect the commercial success of Xerava are increased resistance trends, changes in the reimbursement landscape, and the approval/availability of rapid diagnostics.

We are selling Xerava as an IV antibiotic for use as a first-line empiric monotherapy for the treatment of cIAI. Xerava competes with a number of antibiotics that are currently marketed for the treatment of cIAI and other multidrug resistant infections, including meropenem, which is marketed by AstraZeneca as Merrem, imipenem/cilastatin, which is marketed by Merck & Co., or Merck, as Primaxin, tigecycline, which is marketed by Pfizer as Tygacil, piperacillin/tazobactam, which is marketed by Pfizer as Zosyn, ceftolozane/tazobactam, which is marketed by Merck as Zerbaxa, and ceftazidime/avibactam, which is marketed by Allergan, Inc., and AstraZeneca as Avycaz, meropenem and vaborbactam, which is marketed by Melinta Therapeutics as Vabomere, In addition, there are several antibiotics currently in phase 3 development for cIAI such as sulopenem being developed by Iterum Therapeutics; azetronam/avibactam being developed by Pfizer; and imipenem/relebactam being developed by Merck & Co. We also expect that Xerava will compete with future and current generic versions of marketed antibiotics.

We believe that Xerava may compete effectively against these compounds on the basis of:

- broad range of activity against a wide variety of resistant and MDR Gram-negative, Gram-positive and anaerobic bacteria;
- lower probability of drug resistance;
- a favorable safety and tolerability profile;

- effectiveness in patients with allergies to beta-lactam;
- a convenient dosing regimen with no need for adjustment for renal impairment;
- lower risk of C. Difficile;
- approval as a monotherapy; and
- no drug to drug interactions.

17

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local level, and in other countries, extensively regulate, among other things, the research, development, clinical trials, testing, manufacture, including any manufacturing changes, authorization, pharmacovigilance, adverse event reporting, recalls, packaging, storage, record keeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products and product candidates such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

U.S. Government Regulation

In the United States, the FDA regulates drugs and drug products under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending new drug applications, or NDAs, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil and/or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practice, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- submission to the FDA of an NDA for a drug product which includes not only the results of the clinical trials but also detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labelling for one or more proposed indication(s);
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- payment of user fees and FDA review and approval of the NDA, including consideration of the views of any FDA advisory committee; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct post-approval studies required by the FDA.

Preclinical Studies

Before an applicant begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as other studies to evaluate, among other things, the toxicity of the product

candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long-term toxicity studies, may continue after the IND is submitted.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, must be submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an NDA. The final rule provides that such studies must be conducted in accordance with good clinical practice, or GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA’s regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB’s requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee, or DSMB. This group provides recommendations as to

whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Information about clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called “compassionate use,” is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

On December 13, 2016, the 21st Century Cures Act established (and the 2017 Food and Drug Administration Reauthorization Act later amended) a requirement that sponsors of one or more investigational drugs for the treatment of a serious disease(s) or condition(s) make publicly available their policy for evaluating and responding to requests for expanded access for individual patients. Although these requirements were rolled out over time, they have now come into full effect. This provision requires drug and biologic companies to make publicly available their policies for expanded access for individual patient access to products intended for serious diseases. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study; or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Human Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial along with the requirement to ensure that the data and results reported from the clinical trials are credible and accurate. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the criteria for determining subject eligibility, the dosing plan, the parameters to be used in monitoring safety, the procedure for timely reporting of adverse events, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB representing each clinical site participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that site. The FDA may impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their www.clinicaltrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- Phase 1: The drug is initially introduced into a limited number of healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness. During phase 1 clinical trials, sufficient information about the investigational drug’s or biological product’s pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid phase 2 clinical trials.

- Phase 2: The drug is administered to a larger, but still limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted indications and to determine dosage tolerance and optimal dosage. Phase 2 clinical trials are typically well-controlled and closely monitored.
- Phase 3: The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product. Phase 3 clinical trials usually involve a larger number of participants than a phase 2 clinical trial.

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as phase 4 clinical trials. These studies are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group and to further document a clinical benefit in the case of drugs approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting phase 4 clinical trials could result in withdrawal of approval for products.

Progress reports detailing the status and a brief description of available results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, phase 2 and phase 3 clinical trials may not be completed successfully within any specified period or completed at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product has been associated with unexpected serious harm to patients. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

Marketing Approval

Assuming successful completion of the required clinical testing and other requirements, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has a goal of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to FDA because the FDA has approximately two months to make a "filing" decision. The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

Furthermore, the FDA is not required to complete its review within the established ten-month timeframe and may extend the review process by issuing requests for additional information or clarification.

In addition, under the Pediatric Research Equity Act of 2003, as amended and reauthorized, certain NDAs or supplements to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements.

Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation. Our product candidates are not designated as orphan drugs.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, to mitigate any identified or suspected serious risks. The REMS plan could 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.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. An advisory committee is typically a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with GCP.

The FDA generally accepts data from foreign clinical trials in support of an NDA if the trials were conducted under an IND. If a foreign clinical trial is not conducted under an IND, the FDA nevertheless may accept the data in support of an NDA if the study was conducted in accordance with GCP and the FDA is able to validate the data through an on-site inspection, if deemed necessary. The FDA also expects an explanation of how the foreign data are applicable to the United States population and United States medical practice.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and each may take several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications, and potentially subject to additional restrictions such as a REMS. A complete response letter generally contains a statement of specific deficiencies in the NDA and conditions that must be met in order to secure final approval of the NDA, which may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including phase 4 clinical trials, be conducted to further assess a drug’s safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, certain manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including fast track designation, accelerated approval and priority review, that are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life-threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need, or if the drug qualifies as a QIDP under the recently enacted Generating Antibiotic Incentives Now, or GAIN, Act. The FDA will determine that a product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy in a number of different

ways. Fast track designation provides additional opportunities for interaction with the FDA's review team and may allow for rolling review of NDA components before the completed application is submitted.

The FDA may give a priority review designation to drugs that offer major advances in treatment for a serious condition or provide a treatment where no adequate therapy exists. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. Under the new PDUFA agreement, these six and ten month review periods are measured from the "filing" date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission.

In addition, products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, meaning that it may be approved on (1) the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or (2) on an intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to expedited withdrawal procedures.

Moreover, under the provisions of the Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, a sponsor can request designation of a product candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The benefits of breakthrough therapy designation include much of the same benefits as fast track designation, plus intensive guidance from FDA to ensure an efficient drug development program and organizational commitment involving senior FDA managers.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Limited Population Antibacterial Drug Pathway

With passage of the Cures Act, Congress authorized the FDA to approve an antibacterial or antifungal drug, alone or in combination with one or more other drugs, as a "limited population drug." To qualify for this approval pathway, the drug must be intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs; the standards for approval of drugs and biologics under the FDCA and the Public Health Service Act, or PHSA, must be satisfied; and the FDA must receive a written request from the sponsor to approve the drug as a limited population drug pursuant to this provision. The FDA's determination of safety and effectiveness for such a product must reflect the benefit-risk profile of such drug 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 in such a limited population.

Any drug or biologic approved under this pathway must be labeled with the statement "Limited Population" in a prominent manner and adjacent to the proprietary name of the drug or biological product. The prescribing information must also state that the drug is indicated for use in a limited and specific population of patients and copies of all promotional materials relating to the drug must be submitted to the FDA at least 30 days prior to dissemination of the materials. If the FDA subsequently approves the drug for a broader indication, the agency may remove any post-marketing conditions, including requirements with respect to labeling and review of promotional materials applicable to the product. Nothing in this pathway to approval of a limited population drug prevents sponsors of such products from seeking designation or approval under other provisions of the FDCA, such as accelerated approval.

Post-Approval Regulation

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record keeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval,

many changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. 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 area of production and quality control to maintain cGMP compliance.

The FDA strictly regulates the marketing, labeling, advertising and promotion of drug products that are placed on the market. A product cannot be commercially promoted before it is approved, and approved drugs may generally be promoted only for their approved indications. Promotional claims must also be consistent with the product's FDA-approved label, including claims related to safety and effectiveness. The FDA restricts drug manufacturers' communications regarding uses not described in the FDA-approved labeling, known as off-label uses. The FDA and other federal agencies also closely regulate the promotion of drugs in specific contexts such as direct-to-consumer advertising, industry-sponsored scientific and education activities, and promotional activities involving the Internet and social media.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences of regulatory non-compliance include, among other things:

- restrictions on, or suspensions of, the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- interruption of production processes, including the shutdown of manufacturing facilities or production lines or the imposition of new manufacturing requirements;
- warning letters or other enforcement letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
    - product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil penalties or criminal prosecution.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or 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.

Exclusivity and Approval of Competing Products

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are "abbreviated" because they generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to an RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

The FDA must establish a priority review track for certain generic drugs, requiring the FDA to review a drug application within eight months for a drug that has three or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA's drug shortage list. The new legislation also authorizes FDA to expedite review of ''competitor generic therapies'' or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the applicant is not seeking approval).

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

Qualified Infectious Disease Product Exclusivity

Under the GAIN provisions of FDASIA, which was signed into law in July 2012, the FDA may designate a product as a "qualified infectious disease product," or QIDP. In order to receive this designation, a drug must qualify as an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by either (1) an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens, or (2) a so-called "qualifying pathogen" found on a list of potentially dangerous, drug-resistant organisms to be established and maintained by the FDA. A sponsor must request such designation before submitting a marketing application. We obtained a QIDP designation for the IV formulation of Xerava for cIAI in July 2013, the oral formulation in March 2014, the IV formulation of TP-271 in September 2015, the oral formulation of TP-271 in February 2017, and expect to request QIDP designations for our other product candidates prior to submitting a marketing application for such product candidates, as appropriate.

Upon approving an application for a qualified infectious disease product, the FDA will extend by an additional five years any non-patent marketing exclusivity period awarded, such as a five-year exclusivity period awarded for a new molecular entity. This extension is in addition to any pediatric exclusivity extension awarded, and the extension will be awarded only to a drug first approved on or after the date of enactment.

The GAIN provisions prohibit the grant of an exclusivity extension where the application is a supplement to an application for which an extension is in effect or has expired, is a subsequent application for a specified change to an approved product, or is an application for a product that does not meet the definition of qualified infectious disease product based on the uses for which it is ultimately approved.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, FDA will meet early in the development process to discuss pediatric study plans with sponsors and FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than 90 days after FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA Reauthorization Act of 2017 established new requirements to govern certain molecularly targeted cancer indications. Any company that submits an NDA three years after the date of enactment of that statute must submit pediatric assessments with the NDA if the drug is intended for the treatment of an adult cancer and is directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. The investigation must be designed to yield clinically meaningful pediatric study data regarding the dosing, safety and preliminary efficacy to inform pediatric labeling for the product.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of a clinical investigation involving human beings is begun and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The United States Patent and Trademark Office reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials, marketing authorization, safety reporting and commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of foreign countries or economic areas, such as the EU, before we may commence clinical trials or market products in those countries or areas. The approval process and requirements governing the conduct of clinical trials, product authorization, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

Under EU regulatory systems, a company may submit an application for marketing authorization through several different procedures. These are the centralized, mutual recognition procedure, decentralized procedure, or national procedure (single EU Member State). The centralized procedure is compulsory for medicinal products produced by biotechnology or those medicinal products containing new active substances for specific indications such as the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, viral diseases and designated orphan medicinal products. The centralized marketing authorization procedure is optional for medicinal products containing a new active substance that is not yet authorized in the EEA or for products that constitute a significant therapeutic, scientific or technical innovation or for which grant of centralized marketing authorization is in the interest of patients in the EU. Under the centralized procedure, an application for marketing authorization is submitted to the European Medicines Agency, or EMA, where it will be evaluated by the Committee for Medicinal Products for Human Use and a favorable opinion typically results in the grant by the European Commission of a single marketing authorization that is valid for all European Union Member States and three of the four European Free Trade Association, or EFTA, countries (Iceland, Liechtenstein and Norway). The initial marketing authorization is valid for five years. The authorization may be renewed and remain valid for an unlimited period unless the national competent authority or the European Commission decides on justified grounds to proceed with one additional five-year renewal period. The

renewal of a marketing authorization is subject to a re-evaluation of the risk-benefit balance of the product by the national competent authorities or the EMA. The decentralized authorization procedure permits companies to file identical applications for authorization simultaneously in several EU Member States for a medicinal product that has not yet been authorized in any EU Member State. The competent authorities of a single EU Member State, the reference member state, is appointed to review the application and provide an assessment report. The competent authorities of the other EU Member States, the concerned member states, are subsequently required to grant marketing authorization for their territories on the basis of this assessment. The only exception to this is where an EU Member State considers that there are concerns of potential serious risk to public health related to authorization of the product. In these circumstances, the matter is submitted to the Heads of Medicines Agencies, or CMDh for review. The mutual recognition procedure allows companies that have a medicinal product already authorized in one EU Member State to apply for this authorization to be recognized by the competent authorities in other EU Member States.

In the EU, innovative medicinal products that are subject to marketing authorization on the basis of a full dossier qualify for eight years of data exclusivity from the data of marketing authorization and 10 years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic application or biosimilar application for eight years from the data of authorization of the innovative product. After this period an application for marketing authorization for a generic or biosimilar product may be submitted, and the innovator's data may be referenced. However, even if authorization is granted in relation to the generic product or biosimilar product this product cannot be marketed in the EU until 10 years after grant of authorization for the innovative product. The ten year market exclusivity period may be extended for a further year to a maximum of 11 years if, during the first eight years following authorization of the innovative product, authorization is granted for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

The holder of an EU marketing authorization for a medicinal product must comply with EU pharmacovigilance legislation. This includes requirements to conduct pharmacovigilance, and to assess and monitor the safety of medicinal products.

Various requirements apply to the manufacturing and placing of medicinal products on the EU market. Manufacture of medicinal products in the EU requires a manufacturing authorization. The manufacturing authorization holder must comply with requirements set out in the applicable EU laws, regulations and guidance. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and APIs. These obligations extend to the manufacture of APIs outside of the EU for import into the EU. Similarly, the distribution of medicinal products into and within the EU is subject to compliance with the applicable EU laws, regulations and guidelines, including the requirement to hold appropriate authorizations for distribution granted by the competent authorities of the EU Member States. Marketing authorization holders may be subject to civil, criminal or administrative sanctions, including suspension of manufacturing authorization, in case of non-compliance with the EU or EU Member States' requirements applicable to the manufacturing of medicinal products.

In the EU, the advertising and promotion of medicinal products are subject to EU Member States' laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. Breaches of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of medicinal products to the general public and may also impose limitations on promotional activities with healthcare professionals.

Similar to the United States, the various phases of non-clinical and clinical research in the EU are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC has sought to harmonize the EU clinical trials regulatory framework, setting out common rules for the control and authorization of clinical trials in the EU, the EU Member States have transposed and applied the provisions of the Directive in a manner that is often not uniform. This has led to variations in the rules governing the conduct of clinical trials in the individual EU Member States. The EU legislator adopted Regulation (EU) No 536/2014, or the Clinical Trials Regulation in 2014. The new EU Clinical Trials Regulation, which will replace the EU Clinical Trials Directive, introduces a complete overhaul of the existing regulation of clinical trials for medicinal products in the EU, including a new coordinated procedure for authorization of clinical trials that is reminiscent of the mutual recognition procedure for marketing authorization of medicinal products, and increased obligations on sponsors to publish clinical trial results. The Clinical Trials Regulation is expected to start to apply in late 2019 or in 2020.

Clinical trials must currently be conducted in accordance with the requirements of the EU Clinical Trials Directive and applicable good clinical practice standards, as implemented into national legislation by EU Member States. Under the current regime, before a clinical trial can be initiated it must be approved in each of EU Member State where there

is a site at which the trial is to be conducted by two distinct bodies: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs. Under the current regime all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial must be reported to the NCA and ECs of the Member State where they occurred.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation (GDPR), which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Pharmaceutical Insurance Coverage and Reimbursement

Sales of our products will depend, in part, on the availability and extent of coverage and reimbursement by third-party payors, such as government health programs, including Medicare and Medicaid, commercial insurance and managed healthcare organizations. These third-party payors are increasingly challenging the price and limiting the coverage and reimbursement amounts for medical products and services.

The containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The United States government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement, and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our product candidates or a decision by a third-party payor to not cover our product candidates could reduce physician usage of the product candidate and have a material adverse effect on our sales, results of operations and financial condition.

In the United States, the federal government provides health insurance for people who are 65 or older, and certain people with disabilities or certain conditions irrespective of their age, through the Medicare program, which is administered by the Centers for Medicare & Medicaid Services, or CMS. Coverage and reimbursement for products and services under Medicare are determined in accordance with the Social Security Act and pursuant to regulations promulgated by CMS, as well as the agency’s subregulatory coverage and reimbursement guidance and determinations.

Medicaid is a health insurance program for low-income children, families, pregnant women, and people with disabilities that is jointly funded by the federal and state governments, but administered by the states. In general, state Medicaid programs are required to cover drugs and biologicals of manufacturers that have entered into a Medicaid Drug Rebate Agreement, although such drugs and biologicals may be subject to prior authorization or other utilization controls.

In the United States, there have been and continue to be a number of federal and state legislative and regulatory initiatives to expand health care coverage, improve health care quality, and contain health care costs, which could impact our ability to sell our products profitably. For example, the federal Patient Protection and Affordable Care Act,

as amended by the Health Care and Education Reconciliation Act of 2010, known collectively as ACA, substantially changes the way health care is financed by United States governmental and commercial payors, and significantly affects the United States pharmaceutical industry. Among other things, the ACA establishes annual fees and taxes to be paid by manufacturers of certain branded prescription drugs; creates a new Medicare Part D coverage gap discount program, under which, as a condition of coverage of their products under Medicare Part D, manufacturers currently must agree to offer 70% point-of-sale discounts off of negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period; increases manufacturer rebate liabilities under the Medicaid Drug Rebate Program for outpatient drugs dispensed to Medicaid recipients; addresses a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are injected, inhaled, infused, instilled, or implanted, and for line extensions of current drugs; and expands oversight and support for the federal government’s comparative effectiveness research of services and products.

Some of the provisions of the ACA have yet to be fully implemented, and certain provisions have been subject to judicial or Congressional challenges. In addition, there have been efforts by the Trump Administration to repeal or replace certain aspects of the ACA, and to alter the implementation of the ACA and related laws. And legislation affecting implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017 includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, commonly referred to as the "individual mandate." Additionally, on January 22, 2018, President Trump signed into law a continuing resolution on appropriations for fiscal year 2018 that, among other things, delayed the implementation of certain ACA-mandated fees, including the annual fee imposed on certain high-cost employer-sponsored health plans, commonly referred to as the "Cadillac" health plan tax; the annual fee imposed on certain health insurance providers based on market share; and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amended the ACA, effective January 1, 2019, to reduce the coverage gap in most Medicare prescription drug plans, commonly referred to as the "donut hole." Additional legislative changes, regulatory changes, and judicial challenges related to the ACA remain possible. It is unclear how the ACA and its implementation, as well as efforts to repeal or replace, or invalidate, the ACA, or portions thereof, will affect our business. We participate in and have certain price reporting obligations to the Medicaid Drug Rebate Program and other governmental pricing programs, and we have obligations to report the average sales price for certain of our drugs to the Medicare program. The Medicaid Drug Rebate Program and other governmental programs impose obligations to report pricing figures to the federal government and we are subject to these price reporting and other compliance obligations. Other programs impose limits on the price we are permitted to charge certain entities for our products. Statutory and regulatory changes or other agency action regarding these programs and their requirements could negatively affect the coverage and reimbursement by these programs of our products and could negatively impact our results of operations.

Under the Medicaid Drug Rebate Program, we are required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having federal funds being made available to the state for our drugs under Medicaid and Medicare Part B. Those rebates are based on pricing data reported by us on a monthly and quarterly basis to CMS, the federal agency that administers the Medicare and Medicaid programs. These data include the average manufacturer price and, in the case of innovator products, the best price for each drug, which, in general, represents the lowest price available from the manufacturer to any entity in the United States in any pricing structure, calculated to include all sales and associated rebates, discounts, and other price concessions. The ACA made significant changes to the Medicaid Drug Rebate program, and CMS issued a final regulation, which became effective on April 1, 2016, to implement the changes to the Medicaid Drug Rebate Program under the ACA. Our failure to comply with these price reporting and rebate payment options could negatively impact our financial results.

Federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the Public Health Service's 340B drug pricing discount program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B drug pricing program, which is administered by the Health Resources and Services Administration, or HRSA, requires participating manufacturers to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the average manufacturer price and rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate Program, and in general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. Changes to the definition of average manufacturer price and the Medicaid Drug Rebate amount under the ACA or otherwise also could affect our 340B ceiling price calculations and negatively impact our results of operations.

HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, which became effective on January 1, 2019. HRSA also has announced that it will begin to implement a ceiling price reporting requirement related to the 340B program during the first quarter of 2019. It is currently unclear how HRSA will apply its enforcement authority under the new regulation. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in the inpatient setting.

Federal law also requires that a company that participates in the Medicaid Drug Rebate Program report average sales price information each quarter to CMS for certain categories of drugs that are paid under the Medicare Part B program. Manufacturers calculate the average sales price based on a statutorily defined formula as well as regulations and interpretations of the statute by CMS. CMS uses these submissions to determine payment rates for drugs under Medicare Part B. Statutory or regulatory changes or CMS guidance could affect the average sales price calculations for our products and the resulting Medicare payment rate, and could negatively impact our results of operations. Also, the Medicare Part B drug payment methodology is subject to change based on potential demonstration projects undertaken by CMS or potential legislation enacted by Congress.

Pricing and rebate calculations vary across products and programs, are complex and are often subject to interpretation by us, governmental or regulatory agencies and the courts. The Medicaid rebate amount is computed each quarter based on our submission to CMS of our average manufacturer prices and best prices for the quarter. If we become aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we are obligated to resubmit the corrected data for up to three years after those data originally were due. Such restatements and recalculations would increase our costs for complying with the laws and regulations governing the Medicaid Drug Rebate Program and could result in an overage or underage in our rebate liability for past quarters. Price recalculations also may affect the ceiling price under the 340B program.

We could be held liable for errors associated with our submission of pricing data. Civil monetary penalties can be applied if we are found to have knowingly submitted any false price information to the government, if we are found to have made a misrepresentation in the reporting of our average sales price, if we fail to submit the required price data on a timely basis, or if we are found to have charged 340B covered entities more than the statutorily mandated ceiling price. Such conduct also could be grounds for CMS to terminate our Medicaid drug rebate agreement, in which case federal payments may not be available under Medicaid or Medicare Part B for our covered outpatient drugs. We cannot assure you that our submissions will not be found by CMS to be incomplete or incorrect.

In order to be eligible to have our products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by certain federal agencies and grantees, we participate in the U.S. Department of Veterans Affairs, or VA, Federal Supply Schedule, or FSS, pricing program. Under this program, we are obligated to make our innovative products available for procurement on an FSS contract under which we must comply with standard government terms and conditions and charge a price to certain federal agencies that is no higher than the statutory Federal Ceiling Price, or FCP. The FCP is based on the non-federal average manufacturer price, or Non-FAMP, which we calculate and report to the VA on a quarterly and annual basis.

Pricing and rebate calculations vary across products and programs, are complex, and are often subject to interpretation by us, governmental or regulatory agencies and the courts. Risks relating to price reporting and payment obligations under the foregoing programs are further discussed in the risk factor under the heading, “If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate program or other governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.”

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, in the EU, the sole legal instrument at the EU level governing the pricing and reimbursement of medicinal products is Council Directive 89/105/EEC, or the Price Transparency Directive. The aim of this Directive is to ensure that pricing and reimbursement mechanisms established in the EU Member States are transparent and objective, do not hinder the free movement of and trade in medicinal products in the EU, and do not hinder, prevent or distort competition on the market. The Price Transparency Directive does not provide any guidance concerning the specific criteria on the basis of which pricing and reimbursement decisions are to be made in individual EU Member States, nor does it have any direct consequence for pricing or reimbursement levels in individual EU Member States. The EU Member States are free to restrict the range of medicinal products for which their national health insurance systems provide reimbursement, and to control the prices and/or reimbursement levels of medicinal products for human use. An EU Member State may approve a specific price or level of reimbursement for the medicinal product, or alternatively adopt a system of direct or indirect controls on the profitability of the company responsible for placing the medicinal product on the market, including volume-based arrangements, caps and reference pricing mechanisms.

Health Technology Assessment, or HTA, of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in some EU Member States, including the United Kingdom, France, Germany,

Ireland, Italy and Sweden. The HTA process in the EU Member States is governed by the national laws of these countries. HTA is the procedure according to which the assessment of the public health impact, therapeutic impact, and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. HTA generally focuses on the clinical efficacy and effectiveness, safety, cost, and cost-effectiveness of individual medicinal products as well as their potential implications for the healthcare system. Those elements of medicinal products are compared with other treatment options available on the market. The outcome of HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU Member States. The extent to which pricing and reimbursement decisions are influenced by the HTA of the specific medicinal product vary between EU Member States. A negative HTA of one of our products by a leading and recognized HTA body could not only undermine our ability to obtain reimbursement for such product in the EU Member State in which such negative assessment was issued, but also in other EU Member States. For example, EU Member States that have not yet developed HTA mechanisms could rely to some extent on the HTA performed in countries with a developed HTA framework, such as France, Germany or Sweden, when adopting decisions concerning the pricing and reimbursement of a specific medicinal product.

On January 31, 2018, the European Commission adopted a proposal for a regulation on HTA. This legislative proposal is intended to boost cooperation among EU Member States in assessing health technologies, including new medicinal products, and providing the basis for cooperation at the EU level for joint clinical assessments in these areas. The proposal provides that EU Member States will be able to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU Member States will continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technology, and making decisions on pricing and reimbursement. The European Commission has stated that the role of the draft HTA regulation is not to influence pricing and reimbursement decisions in the individual EU Member States. However, this consequence cannot be excluded.

Healthcare Fraud and Abuse Laws

Healthcare providers, physicians, distributors and third-party payors play a primary role in the distribution, recommendation and prescription of our products. Our arrangements with third-party payors and customers expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements through which we market, sell and distribute our products. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- The United States federal healthcare Anti-Kickback Statute prohibits any person from, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchasing, leasing, ordering or arranging for or recommending of any good or service for which payment may be made, in whole or in part, under federal and state healthcare programs such as Medicare and Medicaid. The term “remuneration” has been broadly interpreted to include anything of value. The Anti-Kickback Statute is subject to evolving interpretation and has been applied by government enforcement officials to a number of common business arrangements in the pharmaceutical industry. The government can establish a violation of the Anti-Kickback Statute without proving that a person or entity had actual knowledge of the statute or specific intent to violate it. There are a number of statutory exemptions and regulatory safe harbors protecting some common activities from prosecution; however, those exceptions and safe harbors are drawn narrowly. Failure to meet all of the requirements of a particular statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute, but the legality of the arrangement will be evaluated on a case-by-case basis based on the totality of the facts and circumstances. We seek to comply with the available statutory exemptions and safe harbors whenever possible, but our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants or patient or product assistance programs.
- The federal civil False Claims Act prohibits, among other things, knowingly presenting, or causing to be presented, claims for payment of government funds that are false or fraudulent, or knowingly making, or using or causing to be made or used, a false record or statement material to a false or fraudulent claim to avoid, decrease, or conceal an obligation to pay money to the federal government. Private individuals, commonly known as “whistleblowers,” can bring civil False Claims Act qui tam actions, on behalf of the government and such individuals and may share in amounts paid by the entity to the government in recovery or settlement. In recent years, several pharmaceutical and other healthcare companies have faced enforcement actions under the federal False Claims Act for, among other things, allegedly submitting false or misleading pricing information to government health care programs and providing free product to customers with the expectation that the customers would bill federal programs for the product. Federal enforcement agencies also have showed increased interest in pharmaceutical companies’ product and patient assistance programs, including reimbursement and co-pay support services, and a number of investigations

into these programs have resulted in significant civil and criminal settlements. Other companies have faced enforcement actions for causing false claims to be submitted because of the company's marketing the product for unapproved, and thus non-reimbursable, uses. In addition, a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. False Claims Act liability is potentially significant in the healthcare industry because the statute provides for treble damages and significant mandatory penalties per false claim or statement for violations. Because of the potential for large monetary exposure, healthcare and pharmaceutical companies often resolve allegations without admissions of liability for significant and material amounts to avoid the uncertainty of treble damages and per claim penalties that may be awarded in litigation proceedings. Companies may be required, however, to enter into corporate integrity agreements with the government, which may impose substantial costs on companies to ensure compliance. Criminal penalties, including imprisonment and criminal fines, are also possible for making or presenting a false, fictitious or fraudulent claim to the federal government.

- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, fraud provisions, among other things, impose criminal and civil liability for knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors. HIPAA also prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false fictitious or fraudulent statement or entry in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal healthcare Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it to have committed a violation.
- The federal Physician Payment Sunshine Act, being implemented as the Open Payments Program, requires certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the United States Department of Health and Human Services, Centers for Medicare and Medicaid Services, information related to payments and other transfers of value, directly or indirectly, to physicians (defined to include doctors, dentists, optometrists, podiatrists, and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives. A manufacturer's failure to submit timely, accurately and completely the required information for all payments, transfers of value or ownership or investment interests may result in civil monetary penalties of up to an aggregate of $150,000 per year, and up to an aggregate of $1 million per year for "knowing failures." Manufacturers must submit reports by the 90th day of each calendar year.

Analogous state laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payors, including private insurers or patients. Several states also require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products in those states and to report gifts and payments to individual health care providers in those states. Some of these states also prohibit certain marketing-related activities, including the provision of gifts, meals, or other items to certain health care providers, and restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs. Some states require the posting of information relating to clinical studies and their outcomes. Some states and cities require identification or licensing of sales representatives. In addition, several states require pharmaceutical companies to implement compliance programs or marketing codes.

Legal Proceedings

In July 2018, a purported securities class action lawsuit was filed against us, our chief executive officer, our chief scientific officer and the underwriters of our July 2017 public offering, in the United States District Court for the Southern District of New York. The complaint is brought on behalf of an alleged class of those who purchased our securities pursuant and/or traceable to our July and August 2017 public offering and those who purchased our securities between March 8, 2017 and February 13, 2018. The complaint purports to allege claims arising under Sections 10 and 20 of the Exchange Act of 1934, as amended, and Sections 11 and 15 of the Securities Act of 1933, as amended. The complaint generally alleges that the defendants violated the federal securities laws by, among other things, making material misstatements or omissions concerning IGNITE3. The complaint seeks, among other relief, unspecified compensatory damages, attorneys' fees, and costs. The defendants have moved to transfer the lawsuit to the United States District Court for the District of Massachusetts. We believe we have valid defenses against these claims, and will engage in a vigorous defense of such litigation.

Employees

As of March 5, 2019, we had 119 full-time employees, 59 of whom were primarily engaged in the commercialization and support of the commercialization of XERAVA and 37 of whom were primarily engaged in research and development activities. A total of 24 employees have an M.D. or Ph.D. degree. None of our employees is represented by a labor union and we consider our employee relations to be good.

Available Information

We file reports and other information with the Securities and Exchange Commission as required by the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act. You can review our electronically filed reports and other information that we file with the SEC on the SEC's web site at http://www.sec.gov.

We were incorporated under the laws of the State of Delaware on July 7, 2006 as Tetraphase Pharmaceuticals, Inc. Our principal executive offices are located at 480 Arsenal Way, Watertown, Massachusetts, 02472, and our telephone number is (617) 715-3600. Our Internet website is http://www.tphase.com. We make available free of charge through our website our Annual Report 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 Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled “Investor Relations,” as a source of information about us.

The foregoing references to our website are not intended to, nor shall they be deemed to, incorporate information on our website into this Annual Report on Form 10-K by reference.

Item 1A. Risk Factors

Our business faces many risks. We caution you that the following important factors, among others, could cause our actual results to differ materially from those expressed in forward-looking statements made by us or on our behalf in this Annual Report on Form 10-K and other filings with the SEC, press releases, communications with investors and oral statements. The risks described below may not be the only risks we face. Additional risks we do not yet know of or which we currently believe are immaterial may also impair our business operations. If any of the events or circumstances described in the following risks actually occurs, our business, financial condition or results of operations could suffer, and the trading price of our common stock could decline.

Risks Relating to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception, expect to incur losses for at least the next several years and may never achieve or sustain profitability.

We have incurred annual net operating losses in every year since our inception. Our net loss was $72.2 million for the year ended December 31, 2018 and $114.8 million for the year ended December 31, 2017. As of December 31, 2018, we had an accumulated deficit of $534.0 million. Prior to October 2018, when we commenced sales of Xerava in the United States, we had not generated any product revenues. For the three months ended December 31, 2018, we generated $0.2 million in net product revenues from sales of Xerava. We have financed our operations primarily through the public offerings and private placements of our equity securities, debt financings, revenue from United States government grants and contract awards and milestone payments from our licensing agreement.

In the third quarter of 2018, we received marketing approval in the United States and in Europe for Xerava for the treatment of complicated intra-abdominal infections, or cIAI. Prior to the marketing approval of Xerava we had devoted substantially all of our financial resources and efforts to research and development, including preclinical and clinical development. With approval of Xerava for cIAI, we believe that we will devote a substantial portion of our financial resources and efforts to supporting the ongoing commercialization of Xerava.

Notwithstanding the initiation of sales of Xerava, we expect to continue to incur significant expenses and operating losses for at least the next several years. The net losses we incur may fluctuate significantly from quarter to quarter. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders’ equity and working capital.

We expect that our expenses will decrease in 2019 compared with 2018, as the lower costs associated with the completion of the IGNITE clinical program will offset increased sales, marketing, distribution and outsourced manufacturing expenses related to the launch of Xerava. Our expenses may also increase if and as we:

- maintain, expand and protect our intellectual property portfolio; and
- in-license or acquire other products and technologies.

Our ability to become and remain profitable depends on our ability to generate revenue. Notwithstanding marketing approval of Xerava in the United States and Europe, we do not expect to generate significant revenue from Xerava sales in the near future. The successful commercialization of Xerava will require us to be effective in a range of challenging activities, including:

- establishing and maintaining sales, pricing, marketing and distribution capabilities to effectively market, sell and be reimbursed for Xerava;
- contracting for the manufacture of sufficient commercial quantities of Xerava; and
- protecting and maintaining our rights to our intellectual property portfolio related to Xerava.

Because of the numerous risks and uncertainties associated with pharmaceutical product development and commercialization, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Our expenses could increase if there are any delays in the development of any of our products or product candidates or delays in the manufacture of any of our products or product candidates, particularly Xerava.

We may be unable to commercialize Xerava or develop and commercialize any additional product candidates and, even if we do, we may never achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business or continue our operations. A decline in the value of our company could cause our stockholders to lose all or part of their investment in us.

We expect that we will need additional funding. If we are unable to raise capital when needed, we could be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We believe that our existing cash and cash equivalents and proceeds from the sales of Xerava will enable us to fund our operating expenses and capital expenditures into the third quarter of 2020. However, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to fund our expenses after that time.

This estimate is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Changing circumstances could cause us to consume capital significantly faster than we currently anticipate, and we may need to spend more money than currently expected because of circumstances beyond our control.

Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- revenue received from commercial sales of Xerava;
- the costs of commercialization activities for Xerava and our product candidates if such additional product candidates receive marketing approval, including the timing and costs of establishing product sales, marketing, distribution and manufacturing capabilities;
- our ability to access the remaining $45.0 million potentially available to us under our Loan and Security Agreement, or the Loan Agreement, with Solar Capital Ltd. as collateral agent and lender and the other lenders named therein (which we refer to collectively as the lenders), dated November 2, 2018;
- the timing and costs of manufacturing activities in connection with the commercialization of Xerava;
- the timing and costs of clinical trials of our product candidates and other development activities;

- the number and characteristics of product candidates that we pursue;
- the terms and timing of any future collaborations, licensing, marketing, distribution or other arrangements that we may establish;

- the amount and timing of any payments we may be required to make, or that we may receive, in connection with the licensing, filing, prosecution, defense and enforcement of any patents or other intellectual property rights, including milestone and royalty payments and patent prosecution fees that we are obligated to pay to Harvard University, or Harvard, and other licenses under license agreements to which we may be a party;
- the costs of maintaining and protecting our intellectual property rights and defending against intellectual property related claims; and
- the extent to which we in-license or acquire other products and technologies.

We have a limited operating history and no history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability.

We began operations in the third quarter of 2006. Our operations to date have been limited to financing and staffing our company, developing our technology and our product candidates and establishing a commercial infrastructure to launch Xerava. We obtained marketing approval for Xerava in the United States and Europe in the third quarter of 2018 and commenced sales of Xerava in the United States in the fourth quarter of 2018. We have not yet demonstrated an ability to conduct sales and marketing activities necessary for successful product commercialization. Consequently, predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

Our level of indebtedness and debt service obligations could adversely affect our financial condition and may make it more difficult for us to fund our operations.

On November 2, 2018, we entered into the Loan Agreement with the lenders. The lenders have agreed to make available to us term loans in an aggregate principal amount of up to $75.0 million under the Loan Agreement. The Loan Agreement provides a term loan commitment of $50.0 million in two potential tranches: (i) a $30.0 million Term A loan facility that was funded on November 2, 2018 and (ii) a $20.0 million Term B loan facility to be funded at the request of the Company, subject to certain conditions being met, no later than October 31, 2020. Both of these term loans have a maturity date of May 2, 2023. The Loan Agreement also provides access to an additional Term C loan facility in the amount of $25.0 million, to be funded at the lenders' sole discretion.

All obligations under the Loan Agreement are secured by substantially all of our existing property and assets. This indebtedness may create additional financing risk for us, particularly if our business or prevailing financial market conditions are not conducive to paying off or refinancing our outstanding debt obligations at maturity. This indebtedness could also have important negative consequences, including:

- the need to repay our indebtedness by making payment of interest only initially and then interest and principal, which will reduce the amount of funds available to finance our operations, our research and development efforts and our general corporate activities; and
- our failure to comply with the restrictive covenants in the Loan Agreement could result in an event of default that, if not cured or waived, would accelerate our obligation to repay this indebtedness, and the lenders could seek to enforce its security interest in the assets securing such indebtedness.

To the extent additional debt is added to our current debt levels, the risks described above could increase.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Currently, our only external committed source of funds is funding under subcontracts awarded to us by CUBRC pursuant to government contracts from BARDA and NIAID, and an award from CARB-X. Although the BARDA contract and our subcontract with CUBRC under the BARDA contract have terms which currently expire on March 30, 2019, BARDA is entitled to terminate the project for convenience at any time and is not obligated to provide

continued funding beyond current-year amounts from congressionally approved annual appropriations. To the extent that BARDA ceases to provide funding of the program to CUBRC, CUBRC has the right to cease providing funding to us. Committed funding from CUBRC under our BARDA subcontract is for up to approximately $41.8 million from the initial contract date through March 30, 2019, of which $39.6 million had been received through December 31, 2018.

Similarly, although the NIAID contract and our subcontract with CUBRC under the NIAID contract have terms which currently expire on March 31, 2019, NIAID is entitled to terminate the project for convenience at any time and is not obligated to provide continued funding beyond March 31, 2019. To the extent NIAID ceases to provide funding of the programs to CUBRC, CUBRC has the right to cease providing funding to us. Committed funding from CUBRC under our subcontract with respect to the NIAID contract is for up to $16.6 million, of which $15.7 million had been received through December 31, 2018.

Similarly, although the CARB-X Award has expired by its terms on December 31, 2018, and we expect to reach an agreement with CARB-X to extend the performance date out to June 30, 2019, CARB-X is entitled to terminate the project for convenience at any time. Committed funding from the CARB-X Award is for up to $4.0 million, of which $1.6 million had been received through December 31, 2018.

Furthermore, we may not be able to access the additional $45.0 million of funding available under the Loan Agreement. Under the terms of the Loan Agreement we may only access $20.0 million of such funds if we meet specific revenue and other milestones and the remaining $25.0 million is only available to us at the discretion of the lenders.

As a result, unless and until we can generate a substantial amount of revenue from Xerava or any other additional product candidates, we expect to finance our future cash needs through public or private equity offerings, debt financings or collaborations and licensing arrangements. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans.

To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, the ownership interest of our stockholders may be materially diluted, and the terms of these securities could include liquidation or other preferences and anti-dilution protections that could adversely affect their rights. In addition, debt financing, if available, would result in increased fixed payment obligations and may involve agreements that include restrictive covenants that limit our ability to take specific corporate actions, such as incurring additional debt, merging with or acquiring another entity, making capital expenditures or declaring dividends, that could adversely impact our ability to conduct our business. In addition, securing additional financing would require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management’s ability to oversee the development and commercialization of our products and product candidates.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, products or product candidates or to grant licenses on terms that may not be favorable to us.

We may not have cash available to us in an amount sufficient to enable us to make interest or principal payments on our indebtedness when due.

We cannot assure you that our business will generate sufficient cash flow from operations or that future borrowings will be available to us under our Loan Agreement or otherwise in an amount sufficient to enable us to repay our indebtedness or fund our other liquidity needs. We may need to refinance all or a portion of our indebtedness, on or before its maturity. We cannot assure you that we will be able to refinance any of our indebtedness on commercially reasonable terms, on a timely basis or at all. Any refinancing of our debt could be at higher interest rates and may require us to comply with more onerous covenants, which could further restrict our business operations. Failure to satisfy our current and future debt obligations could result in an event of default and, as a result, the lenders could accelerate all of the amounts due. In the event of an acceleration of amounts due under the Loan Agreement as a result

of an event of default, we may not have sufficient funds or may be unable to arrange for additional financing to repay our indebtedness. In addition, the lenders could seek to enforce their security interests in the assets securing such indebtedness.

Our ability to make scheduled payments on or to refinance our debt obligations depends on our financial condition and operating performance and the condition of the debt and capital markets, which are subject to prevailing economic, industry and competitive conditions, as well as certain financial, business, legislative, political, regulatory and other factors beyond our control. If our cash flow and capital resources are insufficient to fund our debt service obligations, we could face substantial liquidity problems, be forced to reduce or delay capital expenditures, strategic acquisitions, investments and partnerships, dispose of material assets or operations, seek additional debt or equity capital or restructure or refinance our indebtedness. We cannot assure you that any such actions, if necessary, could be effected on commercially reasonable terms or at all, or on terms that would be advantageous to our stockholders or on terms that would not require us to breach the terms and conditions of our existing or future debt agreements, and our financial position and results of operations could be materially adversely affected.

We are subject to certain restrictive covenants that may restrict our ability to pursue our business strategies, and the failure to comply with such restrictions could materially adversely affect our business.

The Loan Agreement imposes operating and other restrictions on us. Such restrictions will affect, and in many respects limit or prohibit, our ability and the ability of any future subsidiary to, among other things:

- invest in our subsidiaries and make other investments;
- dispose of certain assets;
- change our lines of business;
- engage in mergers or consolidations;
- incur additional indebtedness;
- create liens on assets;
- pay dividends and make distributions or repurchase our capital stock
- amend our material agreements;
- permit our qualified cash subject to a control account in favor of the lenders to be below $10 million plus the amount (if any) of accounts payable aged over 90 days; and
- engage in certain transactions with affiliates.

The restrictions contained in the Loan Agreement could limit our ability to plan for or react to market conditions, meet capital needs or make acquisitions or could otherwise restrict our business and growth strategies, which could materially adversely affect our business, financial condition and operating results. We may not be able to comply with the minimum liquidity covenant.

If we fail to comply with the covenants under the Loan Agreement, we will be in default and, as a result, the lenders could accelerate all of the amounts due.

Risks Related to Product Development and Commercialization

We are dependent on the success of Xerava, and our ability to successfully commercialize Xerava. If we are unable to successfully commercialize Xerava or experience significant delays in doing so, our business could be materially harmed.

We have invested a significant portion of our efforts and financial resources in the development of Xerava for use as a first-line empiric monotherapy for the treatment of multidrug-resistant, or MDR, infections. We obtained marketing approval for Xerava for the treatment of cIAI in the United States and in Europe in the third quarter of 2018. Our prospects are substantially dependent on our ability to successfully commercialize Xerava for the treatment of cIAI. The success of Xerava will depend on several factors, including the following:

- successful commercial launch of Xerava;
- acceptance of Xerava by the medical community, patients and third-party payors;
- obtainment and maintenance of patent and trade secret protection and regulatory exclusivity;
- protection of our rights in our intellectual property portfolio;
- successful manufacturing of Xerava;
- favorable results of any additional clinical trials involving Xerava that we or others may conduct;
- competition with other therapies; and
- a continued acceptable safety profile of Xerava.

If we are unable to successfully commercialize Xerava for the treatment of cIAI our business could be materially harmed.

Xerava or any additional product candidate that we develop and commercialize may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success and the market opportunity for Xerava or any additional product candidates may be smaller than we estimate.

Prior to Xerava, we had never commercialized a product candidate for any indication. Efforts to educate the medical community and third-party payors on the benefits of Xerava or any additional product candidate may require significant resources and may not be successful. If Xerava or any additional product candidate that we develop does not achieve an adequate level of market acceptance, we may not generate significant product revenues and, therefore, we may not become profitable. The degree of market acceptance of Xerava, or any other product candidate that is approved for commercial sale, will depend on a number of factors, including, but not limited to:

- the efficacy and safety of the product;
- the potential advantages of the product compared to alternative treatments, including convenience and ease of administration;
- the prevalence and severity of any side effects;
- the clinical indications for which the product is approved;
- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling or an approved risk evaluation and mitigation strategy;
- our ability to offer the product for sale at competitive prices;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- whether the product is designated under physician treatment guidelines as a first-line therapy or as a second- or third-line therapy for particular infections;
- the strength of marketing and distribution support;
- the approval of other new products for the same indications;
- the timing of market introduction of our approved products as well as competitive products;
- the cost of treatment in relation to alternative treatments;
- availability and level of coverage and amount of reimbursement from government payors, managed care plans and other third-party payors;
- the effectiveness of our sales and marketing efforts;
    - adverse publicity about the product or favorable publicity about competitive products; and
- the development of resistance by bacterial strains to the product.

In addition, the potential market opportunity for Xerava is difficult to estimate. Our estimates of the potential market opportunity are predicated on several key assumptions such as industry knowledge, third-party research reports and other surveys. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management, are inherently uncertain and the reasonableness of these assumptions has not been assessed by an independent source. If any of the assumptions proves to be inaccurate, then the actual market for Xerava could be smaller than our estimates of the potential market opportunity. If the actual market for Xerava is smaller than we expect, or if the product fails to achieve an adequate level of acceptance by physicians, health care payors and patients, our product revenue may be limited, and it may be more difficult for us to achieve or maintain profitability.

If we are unable to successfully establish and maintain sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing Xerava or any product candidate that we develop.

To achieve commercial success for any approved product, including Xerava, we must develop a successful sales and marketing organization or outsource these functions to third parties. We have built a commercial organization in the

United States and recruited experienced sales, marketing and distribution professionals. If we are unable to successfully operate the sales force and maintain marketing and distribution capabilities, our operating results may be adversely affected.

Factors that may inhibit our efforts to commercialize Xerava or any additional product candidates that we develop and commercialize on our own include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the ability of our sales personnel to obtain access to or persuade adequate numbers of physicians to appropriately prescribe any products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines;
- the inability of our medical science group to educate physicians on the benefits to patients of Xerava; and
- unforeseen costs and expenses associated with maintaining an independent sales and marketing organization.

We plan to commercialize Xerava outside the United States with the assistance of collaborators. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of Xerava revenues to us may be lower than if we were to directly market and sell Xerava in those markets. As an example, if Everest Medicines Limited, or Everest Medicines, our collaboration partner for Xerava in certain Asian territories, is unsuccessful in developing and commercializing Xerava in the Chinese market, we may not receive any future milestone or royalty payments. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing Xerava or any other future products.

We face substantial competition from other pharmaceutical and biotechnology companies and our operating results may suffer if we fail to compete effectively.

The development and commercialization of new drug products is highly competitive. We face competition from major pharmaceutical companies, specialty pharmaceutical companies, generic manufacturers and biotechnology companies worldwide with respect to Xerava and to any product candidates that we may seek to develop or commercialize in the future. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products, or are pursuing the development of product candidates, for the treatment of MDR infections. Potential competitors also include academic institutions, government agencies and other public and private research organizations. Our competitors may succeed in developing, acquiring or licensing technologies and drug products that are more effective or less costly than Xerava or any product candidates that we are currently developing or that we may develop, which could render our products and product candidates obsolete or noncompetitive.

There are a variety of available therapies that are generic or marketed for the treatment of cIAI that we would expect would compete with Xerava. The generic agents include piperacillin/tazobactam imipenem/cilastatin, ertapenem, meropenem, doripenem, ampicillin/sulbactam and tigecycline. The marketed products include Zerbaxa and Invanz which are marketed by Merck & Co., Inc., Avycaz which is marketed by Allergan, Inc, and Tygacil which is marketed by Pfizer, Inc. Many of the available therapies are well established and widely accepted by physicians, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic products.

There are also a number of products currently in phase 3 development by third parties to treat MDR infections, including imipenem/relebactam, which is being developed by Merck & Co., Inc.; sulopenem, which is being developed by Iterum Therapeutics; azetronam/avibactam being developed by Pfizer, Inc.; and cefiderocol, which is being developed by Shionogi. If these products are approved, they may also compete with Xerava.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials and obtaining regulatory approvals than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

In July 2012, the Food and Drug Administration Safety and Innovation Act was passed, which included the GAIN Act. The GAIN Act is intended to provide incentives for the development of new, qualified infectious disease products. These incentives may result in more competition in the market for new antibiotics and may cause pharmaceutical and biotechnology companies with more resources than we have to shift their efforts towards the development of products that could be competitive with Xerava and our product candidates.

Even if we are able to commercialize Xerava or any product candidate that we develop, the product may become subject to unfavorable pricing regulations, third-party payor coverage and reimbursement policies or healthcare reform initiatives that could harm our business.

Marketing approvals, pricing, coverage and reimbursement for new drug products vary widely by country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our ability to commercialize Xerava or any other product candidate will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from government authorities, private health insurers, health maintenance organizations and other third-party payors. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. As a result, government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability to sell our product candidates profitably.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. Moreover, obtaining coverage does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the drug and the clinical setting in which it is used. Reimbursement rates may also be based in part on existing reimbursement amounts for lower cost drugs or may be bundled into the payments for other services.

We cannot be sure that coverage will be available for Xerava or any other product candidate that we commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

If clinical trials of any product candidate that we advance to clinical trials fail to demonstrate safety and efficacy to the satisfaction of the FDA or comparable foreign regulatory authorities or do not otherwise produce favorable results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of any product candidate.

We are not permitted to commercialize, market, promote, or sell any product candidate in the United States without obtaining marketing approval from the FDA or in other countries without obtaining approvals from comparable foreign regulatory authorities, such as the EMA, and we may never receive such approvals. We must complete extensive preclinical development and clinical trials to demonstrate the safety and efficacy of our product candidates in humans before we will be able to obtain these approvals. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome.

The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of drug development, including failure to achieve efficacy in a trial or across a broad population of patients, the occurrence of severe adverse events, failure to comply with protocols or applicable regulatory requirements, and determination by the FDA or any comparable foreign regulatory authority that a drug product is not approvable. The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of a clinical trial do not necessarily predict final results. For example, in the first quarter of 2018 we reported top-line data for our IGNITE3 phase 3 clinical trial evaluating the safety and efficacy of Xerava with intravenous, or IV, administration for the treatment of complicated urinary tract infections. IGNITE3 failed to meet the co-primary efficacy endpoints of responder rate (a combination of clinical cure and microbiological success) in the microbiological intent-to-treat population at the end-of-IV treatment visit and at the test-of-cure visit, which were evaluated using a 10% non-inferiority margin. We may fail to achieve success in any future clinical trial of any product candidate.

In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we believe that the results of our clinical trials warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

In some instances, there can be significant variability in safety and/or efficacy results between different trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, adherence to the dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. In addition, in the case of our clinical trials, results may differ on the basis of the type of bacteria with which patients are infected. We cannot be certain that other clinical trials that we may conduct will demonstrate consistent or adequate efficacy and safety to obtain regulatory approval to market our product candidates.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent us from obtaining regulatory approval for any of our product candidates, including:

- clinical trials of our product candidates may produce unfavorable or inconclusive results;
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors, including those manufacturing our product candidates or conducting clinical trials on our behalf, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate;
- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate;
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the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with which we enter into agreement for clinical and commercial supplies;

- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

If we are required to conduct additional clinical trials or other testing of any product candidate that we develop beyond the trials and testing that we contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are unfavorable or are only modestly favorable or if there are safety concerns associated with our product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;
- be subject to additional post-marketing testing or other requirements; or
- remove the product from the market after obtaining marketing approval.

Our product development costs will also increase if we experience delays in testing or marketing approvals and we may be required to obtain additional funds to complete clinical trials. We cannot be certain that our clinical trials will begin as planned or be completed on schedule, if at all, or that we will not need to restructure our trials after they have begun. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do and impair our ability to successfully commercialize our product candidates, which may harm our business and results of operations. In addition, many of the factors that cause, or lead to, clinical trial delays may ultimately lead to the denial of regulatory approval of any product candidate.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue clinical trials for any product candidate that we develop if we are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials for such other product candidate as required by the FDA or comparable foreign regulatory authorities, such as the EMA. Patient enrollment is a significant factor in the timing of clinical trials, and is affected by many factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the proximity of patients to clinical sites;
- the eligibility criteria for the trial;
- the design of the clinical trial; and
- competing clinical trials and clinicians' and patients' perceptions as to the potential advantages and risks of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating.

Serious adverse events or undesirable side effects or other unexpected properties of Xerava or any product candidate may be identified during development or after approval, if obtained, that could delay, prevent or cause the withdrawal of the product candidates' regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if obtained.

Serious adverse events or undesirable side effects caused by, or other unexpected properties of, our product candidates could cause us, an institutional review board, or regulatory authorities to interrupt, delay or halt our clinical trials and could result in a more restrictive label, the imposition of distribution or use restrictions or the delay or denial of regulatory approval by the FDA or comparable foreign regulatory authorities. If any of our product candidates are associated with serious adverse events or undesirable side effects or have properties that are unexpected, we may need to abandon their development or limit development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause undesirable or unexpected side effects that prevented further development of the compound. In our clinical trials of Xerava, some treatment-related adverse events have been reported. The most common treatment-related adverse events observed in clinical trials of Xerava have been nausea and emesis. Additional adverse events, undesirable side effects or other unexpected properties of any of our product candidates could arise or become known either during clinical development or, if approved, after the approved product has been marketed. If such an event occurs during development, our trials could be suspended or terminated, and the FDA or comparable foreign regulatory authorities could order us to cease further development of, or deny approval of, our product candidates. If such an event occurs with respect to Xerava or after an additional product candidate is approved, a number of potentially significant negative consequences may result, including:

- regulatory authorities may withdraw the approval of such product;
- regulatory authorities may require additional warnings on the label or impose distribution or use restrictions;
- regulatory authorities may require one or more post-marketing studies;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product or product candidate, if approved, or could substantially increase commercialization costs and expenses, which could delay or prevent us from generating revenues from the sale of our products and harm our business and results of operations.

Product liability lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of Xerava or of any other products that we may develop.

We face an inherent risk of product liability claims as a result of the clinical testing of our product candidates despite obtaining appropriate informed consents from our clinical trial participants. We face an even greater risk with respect to Xerava or any other product that we sell. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- reduced resources of our management to pursue our business strategy;

- decreased demand for our product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;

- significant costs to defend resulting litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any products that we may develop.

We maintain general liability insurance of $12 million in the aggregate and clinical trial liability insurance of $10 million in the aggregate for all product candidates, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of Xerava and our product candidates, which could adversely affect our business, financial condition and results of operations and prospects.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on our business.

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. From time to time, and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and wastes, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

We maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, but this insurance may not provide adequate coverage against potential liabilities. However, we do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. Current or future environmental laws and regulations may impair our research, development or production efforts, which could adversely affect our business, financial condition, results of operations or prospects. In addition, failure to comply with these laws and regulations may result in substantial fines, penalties or other sanctions.

Our research and development efforts may not result in additional product candidates being discovered on anticipated timelines, which could limit our ability to generate revenues.

Some of our research and development programs are at preclinical stages. Additional product candidates that we may develop or acquire will require significant commitment of resources. We cannot predict whether our research will lead to the discovery and development of any additional product candidates that could generate revenues for us.

Risks Related to Our Dependence on Third Parties

We expect to depend on collaborations with third parties for the development and commercialization of some of our products and product candidates. Our prospects with respect to those products and product candidates will depend in part on the success of those collaborations.

Although we are commercializing Xerava ourselves in the United States, we also intend to seek to commercialize Xerava outside the United States through collaboration arrangements. For instance, in February 2018, we entered into a license agreement with Everest Medicines under which we granted Everest Medicines an exclusive license to develop and commercialize Xerava for the treatment of complicated intra-abdominal infections and other indications, in mainland China and several other Asian territories and countries. In addition, we may seek third-party collaborators for development and commercialization of our product candidates. Our likely collaborators for any marketing, distribution, development, licensing or broader collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. We are not currently party to any such arrangements other than that with Everest Medicines.

We may derive revenue from research and development fees, license fees, milestone payments and royalties under any collaborative arrangement into which we enter. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, our collaborators may have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms. As a result, we can expect to relinquish some or all of the control over the future success of a product or product candidate that we license to a third party.

Collaborations involving our products and product candidates, such as our license arrangement with Everest Medicines, may pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected or in compliance with applicable regulatory requirements;
- collaborators may not pursue development and commercialization of our products and product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- collaborators with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of products and product candidates, might lead to additional responsibilities for us with respect to products and product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of products or product candidates in the most efficient manner or at all. If a collaborator of ours is involved in a business combination, it could decide to delay, diminish or terminate the development or commercialization of any product or product candidate licensed to it by us.

We contract with third parties for the manufacture of Xerava for commercialization and for the manufacture for clinical trials and commercialization of any additional product candidates that we develop and commercialize. This reliance on third parties for manufacturing increases the risk that we will not have sufficient quantities of our product or product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not currently have nor do we plan to build the internal infrastructure or capability to manufacture Xerava or our product candidates for use in the conduct of our clinical trials or for commercial supply. We currently rely on and expect to continue to rely on third-party contract manufacturers to manufacture Xerava and clinical supplies of our product candidates. Further, we have relied on and expect to continue to rely on third-party contract manufacturers to manufacture registration batches and commercial quantities of any product candidate that we commercialize following approval for marketing by applicable regulatory authorities. Reliance on third-party manufacturers entails risks, including:

- delays in the manufacture of our clinical drug supply, registration and validation batches and commercial supply if our third-party manufacturers give greater priority to the supply of other products over our products and product candidates or otherwise do not satisfactorily perform according to the terms of the agreement between us;
- equipment malfunctions, power outages or other general disruptions experienced by our third-party manufacturers to their respective operations and other general problems with a multi-step manufacturing process;
- the possible termination or nonrenewal of the agreement by the third-party at a time that is costly or inconvenient for us;
- the possible breach of the manufacturing agreement by the third-party;
    - the failure of the third-party manufacturer to comply with applicable regulatory requirements; and
- the possible misappropriation of our proprietary information, including our trade secrets and know-how.

We currently rely on a small number of third-party contract manufacturers for all of our required raw materials, drug substance and finished product for our preclinical research and clinical trials. We do not have long-term agreements with any of these third parties. We also do not have any current contractual relationships for the manufacture of commercial supplies of any of our product candidates. If any of our existing manufacturers should become unavailable to us for any reason, we may incur some delay in identifying or qualifying replacements.

We have entered into agreements with third-party contract manufacturers for the commercial production of Xerava and intend to do the same for any additional product candidate that is approved by any regulatory agency. We intend to enter into agreements with third-party contract manufacturers for the commercial production of those products. This process is difficult and time consuming and we may face competition for access to manufacturing facilities, as there are a limited number of contract manufacturers operating under cGMPs that are capable of manufacturing our product candidates. Consequently, we may not be able to reach agreement with third-party manufacturers on satisfactory terms, which could delay our commercialization.

Third-party manufacturers are required to comply with cGMPs and similar regulatory requirements outside the United States. Facilities used by our third-party manufacturers must be inspected by the FDA after we submit a New Drug Application, or NDA, and before potential approval of the product candidate. Similar regulations apply to manufacturers of our product candidates for use or sale in foreign countries. We do not control the manufacturing process and are completely dependent on our third-party manufacturers for compliance with the applicable regulatory requirements for the manufacture of our product candidates. If our manufacturers cannot successfully manufacture material that conforms to the strict regulatory requirements of the FDA and any applicable foreign regulatory authority, they will not be able to secure the applicable approval for their manufacturing facilities. If these facilities are not approved for commercial manufacture, we may need to find alternative manufacturing facilities, which could result in delays in obtaining approval for the applicable product candidate as alternative qualified manufacturing

facilities may not be available on a timely basis or at all. In addition, our manufacturers are subject to ongoing periodic unannounced inspections by the FDA and corresponding state and foreign agencies for compliance with cGMPs and similar regulatory requirements. Failure by any of our manufacturers to comply with applicable cGMPs or other regulatory requirements could result in sanctions being imposed on us or the contract manufacturer, including fines, injunctions, civil penalties, delays, suspensions or withdrawals of approvals, operating restrictions, interruptions in supply and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates and have a material adverse impact on our business, financial condition and results of operations.

Our current and anticipated future dependence upon others for the manufacture of Xerava and any other product candidate that we develop may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

We may have to alter our development and commercialization plans if we are not able to establish collaborations.

We will require additional funds to complete the development and potential commercialization of any product candidates and/or for the development and potential commercialization of Xerava for other indications. For some of our product candidates, we may decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates. For example, we collaborate with Everest Medicines for commercialization of Xerava in certain countries outside the United States. We may not be able to enter into similar arrangements for any additional product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include:

- the likelihood of approval by the FDA or comparable foreign regulatory authorities;
- the potential market for the subject product or product candidate;
- the costs and complexities of manufacturing and delivering such product or product candidate to patients;
- the potential for competing products;
- our patent position protecting the product or product candidate, including any uncertainty with respect to our ownership of our technology or our licensor's ownership of technology we license from them, which can exist if there is a challenge to such ownership without regard to the merits of the challenge;
- the need to seek licenses or sub-licenses to third-party intellectual property; and
- general industry and market conditions.

A collaborator may also consider alternative products, product candidates or technologies for similar indications that may be available for collaboration and whether such collaboration could be more attractive than the one with us for our product or product candidate. We may also be restricted under future license agreements from entering into agreements on certain terms with potential collaborators. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product or product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product or product candidates or bring them to market and our business may be materially and adversely affected.

We rely on third parties to conduct our clinical trials. If they do not perform satisfactorily, our business may be materially harmed.

We do not independently conduct clinical trials of our product candidates. We rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities.

Our reliance on these third parties for clinical development activities limits our control over these activities but we remain responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards. For example, notwithstanding the obligations of a contract research organization for a trial of one of our product candidates, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as current Good Clinical Practices, or cGCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. The FDA enforces these cGCPs through periodic inspections of trial sponsors, principal investigators, clinical trial sites and institutional review boards. If we or our third-party contractors fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA may require us to perform additional clinical trials before approving our product candidates, which would delay the regulatory approval process. We cannot be certain that, upon inspection, the FDA will determine that any of our clinical trials comply with cGCPs. We are also required to register clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, the third parties conducting clinical trials on our behalf are not our employees, and except for remedies available to us under our agreements with such contractors, we cannot control whether or not they devote sufficient time and resources to our ongoing development programs. These contractors may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities, which could impede their ability to devote appropriate time to our clinical programs. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates. If that occurs, we will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates. In such an event, our financial results and the commercial prospects for any additional product candidate that we seek to develop could be harmed, our costs could increase and our ability to generate revenues could be delayed, impaired or foreclosed.

We also rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of any resulting products, producing additional losses and depriving us of potential product revenue.

We rely on third parties to conduct and support our clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We rely on third parties, such as contract research organizations, or CROs, consultants, medical monitors, medical institutions and clinical investigators, to perform and support our clinical trials. Our reliance on these third parties for clinical activities reduces our control over these activities but does not relieve us of our responsibilities, including responsibilities set forth in FDA regulations and guidance. We remain responsible for ensuring that each of our clinical trials is conducted in accordance with such regulations and guidance, as well as with the general investigational plan and protocols for the study and investigator-initiated trials. Moreover, the FDA and equivalent foreign authorities require us to comply with standards, commonly referred to as good clinical practices, or GCP, for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity, and confidentiality of patients in clinical trials are protected. Further, these third parties may also have relationships with other entities, including our competitors for whom they also conduct clinical trials. If these third parties do not successfully carry out their contractual duties or regulatory obligations or meet expected deadlines, if these third parties need to be replaced, or if the quality or accuracy of the data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for other reasons, our pre-clinical development activities or clinical trials may be extended, delayed, suspended, or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our products on a timely basis, if at all, and our business, operating results, and prospects may be adversely affected. Further, our third-party clinical trial investigators and sites may be delayed in conducting our clinical trials for reasons outside of their control. We also rely on third parties to store and distribute supplies, including our products, for our clinical trials, which may require storage and shipment under specific temperature and other environmental conditions. Any performance failure on the part of our existing or future third-party contractors could delay clinical development or regulatory approval of our products or commercialization of our products, producing additional losses and depriving us of potential product revenues.

If we fail to comply with our obligations in the agreements under which we in-license or acquire development or commercialization rights to products or technology from third parties, we could lose commercial rights that are important to our business.

We are a party to a license agreement with Harvard that imposes, and we may enter into additional agreements, including license agreements, with other parties in the future that impose, diligence, development and commercialization timelines, milestone payment, royalty, insurance and other obligations on us. For example, under our license agreement with Harvard, we are obligated to satisfy diligence requirements, including using commercially reasonable efforts to develop and commercialize licensed compounds and to implement a specified development plan, meeting specified development milestones and providing an update on progress on an annual basis. If we fail to comply with these obligations, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product that is covered by these agreements, which could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain sufficient patent protection for our technology, products or our product candidates, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology, products and product candidates may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary chemistry technology, products and product candidates. If we do not adequately protect our intellectual property, competitors may be able to use our technologies and erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we file patent applications in the United States and abroad related to our novel technologies, products and product candidates that are important to our business. The patent application and approval process is expensive and time consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. We may also fail to identify patentable aspects of our research and development before it is too late to obtain patent protection.

Under our license agreement with Harvard, Harvard retains the right to prosecute and maintain specified Harvard patents and patent applications in the field of tetracycline chemistry, which are exclusively licensed to us under the agreement. Moreover, if we license technology or product candidates from third parties in the future, those licensors may retain the right to prosecute, maintain and enforce the patent rights that they license to us with or without our involvement. Because control of prosecution and maintenance rests with Harvard, and prosecution, maintenance and enforcement could rest with future licensors, we cannot be certain that these in-licensed patents and applications will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If Harvard fails to prosecute or maintain, or future licensors fail to prosecute, maintain or enforce, those patents necessary for any of our products or product candidates, our ability to develop and commercialize those products or product candidates may be adversely affected and we may not be able to prevent competitors from making and selling competing products.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. In addition, the determination of patent rights with respect to pharmaceutical compounds and technologies commonly involves complex legal and factual questions, which has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Furthermore, recent changes in patent laws in the United States, including the America Invents Act of 2011, may affect the scope, strength and enforceability of our patent rights or the nature of proceedings which may be brought by us related to our patent rights.

Our pending and future patent applications may not result in patents being issued that protect our technology, products or product candidates, in whole or in part, or that effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

As a result of the America Invents Act of 2011, the United States transitioned to a first-inventor-to-file system in March 2013, under which, assuming the other requirements for patentability are met, the first inventor to file a patent application is entitled to the patent. However, as a result of the lag in the publication of patent applications following filing in the United States, we are not notified and therefore are not able to be certain upon filing that we are the first to file for patent protection for any invention. Moreover, we may be subject to a third-party pre-issuance submission of prior art to the U.S. Patent and Trademark Office, or become involved in opposition, derivation,

reexamination, inter partes review or interference proceedings, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of or invalidate our patent rights, allow third parties to commercialize our technology, products or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may seek to market generic versions of any approved products by submitting Abbreviated New Drug Applications to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable and/or not infringed. Alternatively, our competitors may seek approval to market their own products similar to or otherwise competitive with our products. In these circumstances, we may need to defend and/or assert our patents, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid and/or unenforceable. Even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. For example, in August 2018 we received a Notice of Opposition from the European Patent Office notifying us that one of two European patents we own having claims directed to Xerava had been opposed by a third party. We filed a Response to the Opposition in November 2018 cancelling the opposed claims and maintaining the unopposed claims. Our other European patent covering Xerava is not impacted by the filing of this Opposition and cannot itself be opposed based on its grant date of July 3, 2013. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our patents, trademarks, copyrights or other intellectual property, or those of our licensors. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent’s claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patents do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

In any infringement litigation, any award of monetary damages we receive may not be commercially valuable. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our products and product candidates.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our products and product candidates and use our proprietary chemistry technology without infringing the intellectual property and other proprietary rights of third parties. Numerous third-party United States and non-U.S. issued patents and pending applications exist in the area of antibacterial treatment, including compounds, formulations, treatment methods and synthetic processes that may be applied towards the synthesis of antibiotics. If any of their patents or patent

applications cover our product candidates or technologies, we may not be free to manufacture or market our product candidates as planned. We are aware of a third-party U.S. patent claiming pharmaceutical compositions of tetracyclines. The third-party United States patent could be asserted against us with respect to Xerava. We believe we have defenses in the event that the third party seeks to assert such patent against us, including the invalidity of the relevant claims of such patent. However, we may not be successful in asserting these defenses, including proving invalidity, and could be found to infringe the third party's patent, which would have a material adverse effect on us.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our technology, products or product candidates, including patent infringement litigation with respect to the third-party United States patent referred to above, and Xerava. Other possible adversarial proceedings include interference proceedings before the U.S. Patent and Trademark Office. Third parties may assert infringement claims against us based on existing or future intellectual property rights. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are sued for patent infringement, we would need to

demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could have a material adverse effect on us. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third-party's intellectual property rights, such as the third-party United States patent referred to above, we could be ordered by a court, to cease developing, manufacturing, using, selling or offering for sale the infringing product. Alternatively, we may conclude that we need to obtain a license from such third-party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product or product candidate. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may be subject to claims that we or our employees have misappropriated the intellectual property of a third-party, or claiming ownership of what we regard as our own intellectual property.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees do not use the intellectual property and other proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed such intellectual property or other proprietary information. Litigation may be necessary to defend against these claims.

In addition, while we typically require our employees, consultants and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own. Moreover, because we have licensed intellectual property from Harvard, we must rely on Harvard's practices with regard to the assignment of intellectual property to it. To the extent we or Harvard has failed to obtain such assignments, or such assignments are breached, we may be forced to bring claims against third parties, or defend claims they may bring against us, to determine the ownership of what we regard as our intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our management and scientific personnel.

If we are unable to protect the confidentiality of our trade secrets, the value of our technology could be materially adversely affected, and our business would be harmed.

In addition to seeking patents for some of our technology, products and product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, in seeking to develop and maintain a competitive position. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our consultants, independent contractors, advisors, corporate collaborators, outside scientific collaborators, contract manufacturers, suppliers and other third parties. We, as well as our licensors, also enter into confidentiality and invention or patent assignment agreements

with employees and certain consultants. Any party with whom we or Harvard has executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our business and competitive position could be harmed.

We have not yet completed registration of our trademarks. Failure to secure those registrations could adversely affect our business.

Trademark applications for TETRAPHASE PHARMACEUTICALS, our logo, and combinations of those are allowed in the United States, meaning we can perfect registration once use in commerce has commenced TETRAPHASE PHARMACEUTICALS is either registered or pending in twelve other jurisdictions, the logo is pending or registered in the same twelve jurisdictions, and the combination of the name and logo is pending in three jurisdictions. If we do not secure registrations for our trademarks, we may encounter more difficulty in enforcing them against third parties than we otherwise would, which could adversely affect our business.

We own a pending trademark application in the United States for Xerava, the proprietary name for the Xerava product. A third party has threatened to oppose our application to register this mark and alleges that our use of the Xerava trademark may create a likelihood of confusion and infringe the third party's trademark. We believe we have defenses in the event that the third party opposes our trademark application or seeks to assert its trademark against us.

We own applications to register the Xerava trademark in three jurisdictions outside the United States and the availability of the proposed names for registration and use in foreign jurisdictions is not known. In addition, in the United States Patent and Trademark Office and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to seek to cancel registered trademarks. Cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. We have also obtained registration for our design mark in two jurisdictions, and applications remain pending for those design marks in the United States and one other jurisdiction.

Risks Related to Regulatory Approval and Other Legal Compliance Matters

Clinical development, including the conduct of clinical trials necessary to support an NDA, is a lengthy and expensive process with an uncertain outcome, and results of earlier preclinical studies and clinical trials may not be predictive of future trial results. Delays or failure can occur at any stage of clinical development and may adversely affect our business, operating results, and prospects.

Initiating and completing clinical trials necessary to support approval of our current and future products will be time consuming and expensive and the outcome is uncertain. Clinical testing is expensive and can take many years to complete and its outcome is inherently uncertain. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. Failure can occur at any time and for any number of reasons during the clinical trial process. The results of preclinical studies and early clinical trials and evaluations of our products may not be predictive of the results of later stage clinical trials. Similarly, the final results from a clinical trial may not be as favorable as interim results reported earlier in the same clinical trial. Products in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials.

Our products are in various stages of development. Clinical trial failures may occur at any stage and may result from a multitude of factors both within and outside our control, including flaws in formulation or manufacturing, medical device design, adverse safety or efficacy profile and flaws in trial design, among others. If the trials result in negative or inconclusive results, we or our collaborators may decide, or regulators may require us, to discontinue trials of the products or conduct additional clinical trials or preclinical studies. In addition, data obtained from trials and studies are susceptible to varying interpretations, and we cannot guarantee that the FDA or foreign regulatory authorities will interpret our data the same way that we do, which may delay, limit or prevent regulatory approval or clearance. The FDA or foreign regulatory authorities may also disagree with the design of our clinical trials. To the extent that the results of the trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional trials in support of potential approval of our products. Other potential reasons for clinical trial failures include, but are not limited to, inability to enroll sufficient patients, inability to engage sufficient clinical sites, inability to obtain or maintain institutional review board, or IRB, approval of the trial, or cessation of a trial for futility or safety concerns by us, FDA, or foreign regulatory authorities, or an independent committee such as an independent data monitoring committee. As a result of any number of potential reasons, our current and future clinical trials may not be successful

Development of sufficient and appropriate clinical protocols to demonstrate safety and efficacy are required and we may not adequately develop such protocols to support clearance and approval or the results from such studies may not sufficiently demonstrate safety and efficacy. Further, the FDA or foreign regulatory authorities may, among other things, require us to submit data on a greater number of patients than we originally anticipated and/or for a longer follow-up period or change the data collection requirements or data analysis applicable to our clinical trials. Delays in patient enrollment or failure of patients to continue to participate in a clinical trial may cause an increase in costs and delays in the approval and attempted commercialization of our products or result in the failure of the clinical trial. In addition, despite considerable time and expense invested in our clinical trials, the FDA or other regulatory authority may not consider our data adequate to demonstrate safety and efficacy. Such increased costs and delays or failures could adversely affect our business, operating results and prospects. In addition, many of the factors that cause or lead to a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our products.

If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize any future product candidate that we develop in addition to Xerava, and our ability to generate additional revenue will be materially impaired.

Our future product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, record keeping, labeling, storage, approval, advertising, promotion, marketing, export, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by comparable foreign regulatory authorities, with regulations differing from country to country. Failure to obtain marketing approval for any such future product candidate will prevent us from commercializing such product candidate.

We are not permitted to market our product candidates in the United States until we receive approval of an NDA from the FDA. An NDA must include extensive preclinical and clinical data and supporting information to establish the product candidate's safety and efficacy for each desired indication. The NDA must also include significant information regarding the chemistry, manufacturing and controls for the product candidate. Obtaining approval of an NDA is a lengthy, expensive and uncertain process. The drug development and FDA review process typically takes years to complete. The FDA has substantial discretion in the approval process and may refuse to accept for filing any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies or additional information regarding chemistry, manufacturing and controls for the product candidate. Foreign regulatory authorities have differing requirements for approval of drug candidates with which we must comply prior to marketing. Obtaining marketing approval for marketing of a product candidate in one country does not ensure that we will be able to obtain marketing approval in other countries, but the failure to obtain marketing approval in one jurisdiction could negatively impact our ability to obtain marketing approval in other jurisdictions. Delays in approvals or rejections of marketing applications in the United States or foreign countries may be based upon many factors, including regulatory requests for additional analyses, reports, data and studies, regulatory questions regarding, or different interpretations of, data and results, changes in regulatory policy during the period of product development and the emergence of new information regarding product candidates or related products. The FDA or equivalent foreign regulatory authorities may determine that Xerava or any other product candidate that we develop is not effective, or is only moderately effective, or has undesirable or unintended side effects, toxicities, safety profile or other characteristics that preclude marketing approval or prevent or limit commercial use. The FDA may also find during its pre-approval inspection that the facilities identified in our NDA fail to comply with cGMP requirements, thereby delaying or preventing approval. In addition, any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable. If we experience delays in obtaining approval or if we fail to obtain approval of any product candidate that we develop, the commercial prospects for such product candidate may be harmed and our ability to generate revenues will be materially impaired.

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad. Any approval we are granted for our product candidates in the United States would not assure approval of our product candidates in foreign jurisdictions.

In order to market and sell our products in the European Union and other foreign jurisdictions, we, and any future collaborators, must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The marketing approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, a product must be approved for reimbursement before the product can be approved for sale in that country. We, and any future collaborators, may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by

regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may file for marketing approvals but not receive necessary approvals to commercialize our products in any market.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

We are subject to ongoing obligations and continuing regulatory review following the marketing approval of Xerava, which may result in significant additional expense. Xerava could be subject to restrictions or withdrawal from the market, and we may be subject to penalties, if we fail to comply with regulatory requirements or if we experience unanticipated problems with Xerava or our product candidates, when and if approved.

Xerava is subject to, and any product candidate for which we obtain marketing approval, will also be subject to ongoing regulatory requirements, including for labeling, manufacturing, packaging, storage, distribution, advertising, promotion, record-keeping and submission of safety and other post-market information. For example, approved products, manufacturers and manufacturers' facilities are required to comply with extensive FDA requirements or requirements of equivalent foreign regulatory authorities, including ensuring that quality control and manufacturing procedures conform to cGMPs. As such, we and our contract manufacturers will be subject to continual review and periodic inspections to assess compliance with cGMPs. Accordingly, we and others with whom we work must continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production and quality control. We are also required to report certain adverse reactions and production problems, if any, to the FDA or equivalent foreign authorities and to comply with requirements concerning advertising and promotion for our products.

In addition, even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed, may be subject to significant conditions of approval or may impose requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling and regulatory requirements. The FDA also imposes stringent restrictions on manufacturers' communications regarding uses not described in the FDA-approved label, known as off-label uses, and if we do not restrict the marketing of our products only to their approved indications, we may be subject to enforcement action for off-label promotion.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of a product, it may impose restrictions on that product or us. In addition, if any product fails to comply with applicable regulatory requirements, a regulatory agency may:

- issue warning or untitled letters;
- mandate modifications to promotional materials or require provision of corrective information to healthcare practitioners and patients;
- impose restrictions or requirements on the product or its manufacturers or manufacturing processes or suspension of manufacturing processes;
- impose restrictions on the labeling or marketing of the product;
- impose restrictions on product distribution or use;
- require post-marketing clinical trials;
- require withdrawal of the product from the market;
- refuse to approve pending applications or supplements to approved applications that we submit;
- require recall of the product;
- require entry into a consent decree, which can include imposition of various fines (including restitution or disgorgement of profits or revenue), reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- suspend, vary, modify or withdraw marketing approvals;
- refuse to permit the import or export of the product;
- seize or detain supplies of the product; or
- issue injunctions, levy fines or impose other civil penalties or bring criminal prosecution.

55

A recall of our products, or the discovery of serious safety issues with our products, could have a significant adverse impact on us.

The FDA and equivalent foreign authorities have the authority to require the recall of commercialized drugs in the event of material deficiencies, defects in design or manufacture, or stability failures. Manufacturers may, under their own initiative, recall a product if any material deficiency in a drug is found. A government-mandated or voluntary recall by us or one of our distributors could occur as a result of an unacceptable risk to health, component failures, manufacturing errors, stability failures, drug contamination or impurities, design or labeling defects or other deficiencies and issues. Recalls of any of our products would divert managerial and financial resources and have an adverse effect on our reputation, financial condition and operating results, which could impair our ability to produce our products in a cost-effective and timely manner. The FDA and equivalent foreign authorities require that certain classifications of recalls be reported to them within a defined period of time (within ten working days for the FDA) after the recall is initiated. Companies are required to maintain certain records of recalls, even if they are not reportable to the FDA or equivalent foreign authorities. We may initiate voluntary recalls involving our products in the future that we determine do not require notification of the FDA or equivalent foreign authorities. If the FDA or equivalent foreign authorities disagree with our determinations, they could require us to report those actions as recalls. A future recall announcement could harm our reputation with customers and negatively affect our sales. In addition, the FDA or equivalent foreign authorities could take enforcement action for failing to report the recalls when they were conducted.

An increase in the frequency or severity of adverse events, or repeated product complaints or malfunctions may result in a voluntary or involuntary product recall, which could divert managerial and financial resources, impair our ability to manufacture our products in a cost-effective and timely manner and have an adverse effect on our reputation, financial condition, and operating results.

Any adverse event involving our products could result in future voluntary corrective actions, such as recalls or customer notifications, or regulatory agency action, which could include inspection, mandatory recall or other enforcement action. Any corrective action, whether voluntary or involuntary, will require the dedication of our time and capital, distract management from operating our business and may harm our reputation and financial results.

Our relationships with customers and third-party payors are subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Our arrangements with third-party payors, healthcare professionals and customers who purchase, recommend or prescribe our products and product candidates are subject to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our products, and it is possible that our business activities could be subject to challenge or enforcement under one or more of these laws and regulations. These laws and regulations include the United States federal healthcare Anti-Kickback Statute, the federal civil False Claims Act, [HIPAA], the federal Physician Payments Sunshine Act, and analogous state laws and regulations, and they are described in detail above in “Business U.S. Government Regulation Healthcare Fraud and Abuse Laws”.

The shifting commercial compliance environment and the need to build and maintain robust and expandable systems to comply with different compliance or reporting requirements in multiple jurisdictions increase the possibility that we or our partners may fail to comply fully with one or more of these requirements, and we will be required to spend substantial time and money to ensure that our business arrangements with third parties comply with applicable healthcare laws and regulations. If governmental authorities find that our operations violate any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and

administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and we may be required to curtail or restructure our operations, any of which could adversely affect our ability to operate our business and our financial results. Moreover, we expect that there will continue to be federal and state laws and regulations, proposed and implemented, that could impact our operations and business. The extent to which future legislation or regulations, if any, relating to healthcare fraud and abuse laws or enforcement, may be enacted or what effect such legislation or regulation would have on our business remains uncertain.

Similar restrictions are imposed on the promotion and marketing of medicinal products in the EU Member States and other foreign countries. These include restrictions prohibiting the promotion of a compound prior to its approval. Laws (including those governing promotion, marketing and anti-kickback provisions), industry regulations and professional codes of conduct often are strictly enforced. Even in those countries where we may decide not to directly promote or market our products, inappropriate activity by our international distribution partners could have implications for us.

We also are subject to state and federal laws governing the collection, use, and disclosure and protection of health-related and other personal information, including state security breach notification laws, state health information privacy laws, and federal and state consumer protection laws. Failure to comply with these laws and regulations promulgated thereunder could result in government enforcement actions and create liability, private litigation, or adverse publicity. In addition, we may obtain health information from third parties, such as research institutions, that are subject to privacy and security requirements under HIPAA. Although we are not directly subject to HIPAA – other than with respect to providing certain employee benefits – we could potentially be subject to criminal penalties if we, our affiliates, or our agents knowingly obtain or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA. In addition, HIPAA does not replace federal, state, or other laws that may grant individuals even greater privacy protections.

Current and future legislation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of our product candidates and affect the prices we, or they, may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any collaborators, to profitably sell any products for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any future collaborators, may receive for any approved products.

We expect that existing healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

The costs of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Trump Administration have stated that they will address such costs through new legislative and administrative measures. The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired.

At the same time, the Trump Administration’s budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Additionally, the Trump Administration released a “Blueprint” to lower drug prices and reduce out-of-pocket costs of drugs that contains additional proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out-of-pocket costs of drug products paid by consumers. While any proposed measures will require authorization through additional legislation to become effective, Congress and the Trump Administration have each indicated that it

will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate program or other governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

Reporting and payment obligations under the Medicaid Drug Rebate Program and other governmental programs are described in "Business- Government Regulation and Product Approval – Pharmaceutical Insurance Coverage and Reimbursement" in Part I, Item 1 of this Annual Report on Form 10-K. Our failure to comply with these price reporting and rebate payment obligations could negatively impact our financial results.

CMS issued a final regulation, which became effective on April 1, 2016, to implement the changes to the Medicaid Drug Rebate Program under the ACA. The issuance of the final regulation, as well as any other regulations and coverage expansion by various governmental agencies relating to the Medicaid Drug Rebate Program, has increased and will continue to increase our costs and the complexity of compliance, and could have a material adverse effect on our results of operations, particularly if CMS challenges the approach we take in our implementation of the final regulation.

We also participate in the 340B program, which is more fully described "Business-Government Regulation and Product Approval – Pharmaceutical Insurance Coverage and Reimbursement" in Part I, Item 1 of this Report on Form 10-K. The U.S. Department of Health and Human Services' Health Resources and Services Administration, or HRSA, which administers the 340B program, issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, which became effective on January 1, 2019. It is currently unclear how HRSA will apply its enforcement authority under the new regulation. Implementation of this regulation could affect our obligations and potential liability under the 340B program in ways we cannot anticipate.

We have obligations to report the average sales price for certain of our drugs to the Medicare program, as more fully described "Business Government Regulation and Product Approval-Pharmaceutical Insurance Coverage and Reimbursement" in Part I, Item 1 of this Annual Report on Form 10-K. Statutory or regulatory changes or CMS guidance could affect the average sales price calculations for our products and the resulting Medicare payment rate, and could negatively impact our results of operations.

Pricing and rebate calculations vary across products and programs, are complex, and are often subject to interpretation by us, governmental or regulatory agencies and the courts. In the case of our Medicaid pricing data, if we become aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we are obligated to resubmit the corrected data for up to three years after those data originally were due. Such restatements and recalculations increase our costs for complying with the laws and regulations governing the Medicaid Drug Rebate Program and could result in an overage or underage in our rebate liability for past quarters. Price recalculations also may affect the ceiling price at which we are required to offer our products under the 340B program.

We participate in the U.S. Department of Veterans Affairs, or VA, Federal Supply Schedule, or FSS, pricing program and the Tricare Retail Pharmacy program, as more fully described under the heading "Business-Government Regulation and Product Approval-Pharmaceutical Insurance Coverage and Reimbursement" in Part I of this Annual Report on Form 10-K. Pursuant to applicable law, knowing provision of false information in connection with price reporting under these programs can subject a manufacturer to civil monetary penalties. These program obligations also contain extensive disclosure and certification requirements. If we overcharge the government in connection with our FSS contract or Tricare Agreement, we are required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the False

Claims Act and other laws and regulations. Unexpected refunds to the government, and responding to a government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

We are subject to United States and foreign anti-corruption and anti-money laundering laws with respect to our operations and non-compliance with such laws can subject us to criminal and/or civil liability and harm our business.

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the United States domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and possibly other state and national anti-bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities.

We have adopted a Code of Business Conduct and Ethics that mandates compliance with the FCPA and other anti-corruption laws applicable to our business throughout the world. We cannot assure you, however, that our employees and third-party intermediaries will comply with this code or such anti-corruption laws. Noncompliance with anti-corruption and anti-money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

We are subject to governmental export and import controls that could impair our ability to compete in international markets due to licensing requirements and subject us to liability if we are not in compliance with applicable laws.

Our products and solutions are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, United States Customs regulations, and various economic and trade sanctions regulations administered by the United States Treasury Department's Office of Foreign Assets Controls. Exports of our products and solutions outside of the United States must be made in compliance with these laws and regulations. If we fail to comply with these laws and regulations, we and certain of our employees could be subject to substantial civil or criminal penalties, including the possible loss of export or import privileges; fines, which may be imposed on us and responsible employees or managers; and, in extreme cases, the incarceration of responsible employees or managers.

In addition, changes in our products or solutions or changes in applicable export or import laws and regulations may create delays in the introduction, provision, or sale of our products and solutions in international markets, prevent customers from using our products and solutions or, in some cases, prevent the export or import of our products and solutions to certain countries, governments or persons altogether. Any limitation on our ability to export, provide, or sell our products and solutions could adversely affect our business, financial condition and results of operations.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

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. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

We maintain workers’ compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, but this insurance may not provide adequate coverage against potential liabilities. We do not, however, maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

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

Risks Related to Employee Matters

Our future success depends on our ability to retain our chief executive officer and other key executives and to attract, retain and motivate qualified personnel.

Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the research and development, regulatory, commercialization and business development expertise of our executive management team, as well as the other principal members of our management, scientific and clinical team. Although we have formal employment agreements with our executive officers, these agreements do not prevent them from terminating their employment with us at any time. For instance, in December 2017, our former chief medical officer terminated his employment with us and in March 2018, our former chief financial officer terminated her employment with us.

We do not have formal employment agreements with any of our other employees. If we lose one or more of our executive officers or key employees, our ability to implement our business strategy successfully could be seriously harmed. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize products successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high quality personnel, our ability to develop and commercialize product candidates will be limited.

The business that we conduct outside the United States may be adversely affected by international risk and uncertainties.

Although our operations are based in the United States, we conduct business outside the United States and expect to continue to do so in the future. For instance, many of the sites at which our clinical trials are or may be conducted are outside the United States. In addition, we plan to seek approvals to sell our products in foreign countries. Any business that we conduct outside the United States will be subject to additional risks that may materially adversely affect our ability to conduct business in international markets, including:

- potentially reduced protection for intellectual property rights;
- the potential for so-called parallel importing, which is what happens when a local seller, faced with high or higher local prices opts to import goods from a foreign market (with low or lower prices) rather than buying them locally;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting a product candidate and/or finished drug product supply or manufacturing capabilities abroad;
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters, including earthquakes, hurricanes, typhoons, floods and fires; and
- failure to comply with Office of Foreign Asset Control rules and regulations and the Foreign Corrupt Practices Act.

Our internal computer systems, or those of any collaborators, contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs or overall business operations.

Our internal computer infrastructure and those of any collaborators, contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have precautions in place and have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed, and the further development and commercialization of our product candidates could be delayed or halted.

Our employees may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately, or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions

and serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws, standards or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

Risks Related to Our Common Stock

The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock.

Our stock price may be volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. For example, our stock traded within a range of a high price of $52.90 per share and a low price of $1.01 per share for the period beginning March 20, 2013, our first day of trading on the Nasdaq Global Select Market, through March 13, 2019. As a result of this volatility, investors may not be able to sell their common stock at or above the prices they paid for it. The market price for our common stock may be influenced by many factors, including:

- revenues related to Xerava;
- the filing and approval of marketing applications for our product candidates;
- the timing of clinical trials of our product candidates;
- results of clinical trials of our product candidates;
- regulatory actions by the FDA or equivalent authorities in foreign jurisdictions with respect to Xerava and any other product candidate;
- failure or discontinuation of any of our development programs;
- the success of existing or new competitive products or technologies;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to develop, in-license or acquire additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- announcement or expectation of additional financing efforts or licensing or other strategic transactions;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk Factors” section.

We have been, currently are and may again be subject to class action litigation and have been and may again be subject to shareholder derivative litigation, which could distract our management and could result in substantial costs or large judgments against us.

The stock market frequently experiences extreme price and volume fluctuations. We have experienced significant declines in our stock price following our announcements that IGNITE2 and IGNITE3, our phase 3 clinical trials for Xerava for the treatment of patients with cUTI, did not meet the primary endpoints of those trials. In addition, the market prices of securities of companies in the biotechnology and pharmaceutical industry have been extremely volatile and have experienced fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. These fluctuations could adversely affect the market price of our common stock. In the past, securities class action litigation has often been brought against companies following periods of volatility in the market prices of their securities. For instance, in January 2016 and March 2016, two class action lawsuits were filed against us, our chief executive officer and certain former executives in the United States District Court for the District of Massachusetts. These cases were subsequently consolidated. In November 2017 plaintiffs withdrew a pending appeal in the United States Court of Appeals for the First Circuit. In addition, in May 2016, a shareholder derivative action was filed against our chief executive officer, certain former executive officers, all the members of our current board of directors, a former board member, and against us as nominal defendant, in Massachusetts Superior Court (Suffolk County). This case was subsequently dismissed by the court without prejudice due to the plaintiff's failure to properly perfect service of process. Furthermore, in July 2018 a class action lawsuit was filed against us, or chief executive officer, our chief scientific officer and other third parties in the United States District Court for the Southern District of New York in connection with the failure of IGNITE3 to meet its co-primary endpoints. Due to the volatility in our stock price, we may be the target of similar litigation in the future.

In connection with our current litigation and any such future litigation, we could incur substantial costs and such costs, and any related settlements or judgments may not be covered by insurance. We could also suffer an adverse impact on our reputation and a diversion of management's attention and resources, which could cause serious harm to our business, operating results and financial condition.

An active trading market for our common stock may not be sustained.

Although we have listed our common stock on the Nasdaq Global Select Market, an active trading market for our common stock may not be sustained. In the absence of an active trading market for our common stock, investors may not be able to sell their common stock at or above the price at which they acquired the common stock or at the times that they would like to sell. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our common stock will depend on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us, or provide favorable coverage. If one or more analysts downgrade our stock or change their opinion of our stock, our share price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

We have broad discretion in the use of our cash reserves and may not use them effectively.

Our management has broad discretion to use our cash reserves and could spend these reserves in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our products and product candidates. Pending their use, we may invest our cash reserves in a manner that does not produce income or that loses value.

Failure to maintain effective internal controls in accordance with Section 404 of the Sarbanes-Oxley Act in the future could have a material adverse effect on our ability to produce accurate financial statements and on our stock price.

Section 404 of the Sarbanes-Oxley Act of 2002 requires us, on an annual basis, to review and evaluate our internal controls. To maintain compliance with Section 404, we are required to document and evaluate our internal control over financial reporting, which has been both costly and challenging. We will need to continue to dedicate internal resources, continue to engage outside consultants and follow a detailed work plan to continue to assess and document the adequacy of internal control over financial reporting, continue to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. There is a risk that in the future neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

We do not anticipate paying any cash dividends on our capital stock in the foreseeable future; accordingly, stockholders must rely on capital appreciation, if any, for any return on their investment.

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the operation, development and growth of our business. The terms of the Loan Agreement precluded us from paying dividends, and any future debt agreements may also preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our by-laws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that all members of the board are not elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted on at stockholder meetings;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call a special meeting of stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a “poison pill” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
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require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or by-laws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. This could discourage, delay or prevent someone from acquiring us or merging with us, whether or not it is desired by, or beneficial to, our stockholders.

ITEM 1B. Unresolved Staff Comments
None.

ITEM 2. Properties
We lease our principal facilities, which consist of approximately 37,438 square feet of office, research and laboratory space located at 480 Arsenal Way, Watertown, Massachusetts. The leases covering this space expire on November 30, 2022. We believe that our existing facilities are sufficient for our current needs. In the third quarter of 2016, we entered into a sublease with respect to a portion of our principal facilities with an unrelated third party. The term of the sublease expires in November 2019.

ITEM 3. Legal Proceedings
In July 2018, a purported securities class action lawsuit was filed against us, our chief executive officer, our chief scientific officer and the underwriters of our July 2017 public offering, in the United States District Court for the Southern District of New York. The complaint is brought on behalf of an alleged class of those who purchased our securities pursuant and/or traceable to our July and August 2017 public offering and those who purchased our securities between March 8, 2017 and February 13, 2018. The complaint purports to allege claims arising under Sections 10 and 20 of the Exchange Act of 1934, as amended, and Sections 11 and 15 of the Securities Act of 1933, as amended. The complaint generally alleges that the defendants violated the federal securities laws by, among other things, making material misstatements or omissions concerning IGNITE3. The complaint seeks, among other relief, unspecified compensatory damages, attorneys' fees, and costs. The defendants have moved to transfer the lawsuit to the United States District Court for the District of Massachusetts. We believe we have valid defenses against these claims, and will engage in a vigorous defense of such litigation.

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

Market Information

Our common stock began trading on the Nasdaq Global Select Market on March 20, 2013 under the symbol "TTPH". Prior to that date, there was no established public trading market for our common stock.

Holders

At March 5, 2019, there were approximately 8 holders of record of our common stock. We believe that the number of beneficial owners of our common stock at that date was substantially greater.

Dividends

We have never declared or paid any cash dividends on our common stock we are currently prohibited from paying cash dividends under the terms of our debt facility with Solar Capital. We currently intend to retain earnings, if any, for use in our business and do not anticipate paying cash dividends on our common stock in the foreseeable future. Payment of future dividends, if any, on our common stock will be at the discretion of our board of directors after taking into account various factors, including our financial condition, operating results, anticipated cash needs, and plans for expansion.

Securities Authorized for Issuance under Equity Compensation Plans

The information required by this item will be set forth in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

Purchase of Equity Securities

We did not purchase any of our equity securities during the period covered by this Annual Report on Form 10-K.

Unregistered Sales of Equity Securities

None

Comparative Stock Performance Graph

The information included under the heading "Comparative Stock Performance Graph" in this Item 5 of Part II of this Annual Report on Form 10-K shall not be deemed to be "soliciting material" or subject to Regulation 14A or 14C, shall not be deemed "filed" for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act.

65

Set forth below is a graph comparing the total cumulative returns of Tetraphase, the Nasdaq Composite Index and the Nasdaq Biotechnology Index. The graph assumes $100 was invested on March 20, 2013 in our common stock and each of the indices and that all dividends, if any, are reinvested.

	3/20/13	12/31/13	12/31/14	12/31/15	12/31/16	12/31/17	12/31/18
Tetraphase Pharmaceuticals	$100.00	$193.14	$567.29	$143.29	$57.57	$90.00	$16.14
NASDAQ Composite Index	$100.00	$128.34	$145.54	$153.88	$165.42	$212.14	$203.90
NASDAQ Biotechnology Index	$100.00	$145.52	$195.14	$217.43	$170.28	$206.14	$186.91

ITEM 6. Selected Financial Data

No disclosure required.

ITEM 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes appearing in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a biopharmaceutical company using our proprietary chemistry technology to create, develop and commercialize novel tetracyclines for serious and life-threatening conditions, including bacterial infections caused by many multidrug-resistant, or MDR, bacteria. There is a medical need for new antibiotics as resistance to existing antibiotics increases. In recognition of this need, we developed our product Xerava™ (eravacycline), a fully synthetic fluorocycline, as an intravenous, or IV antibiotic for use as a first-line empiric monotherapy for the treatment of MDR infections, including MDR Gram-negative infections, such as those found in complicated intra-abdominal infections, or cIAI.

On August 27, 2018, the United States Food and Drug Administration, or FDA, approved Xerava for the treatment of cIAI in adults. Approval of Xerava was based on our IGNITE (Investigating Gram-Negative Infections Treated with Eravacycline) phase 3 program. In the first pivotal phase 3 trial in the IGNITE program in patients with cIAI, twice-daily intravenous (IV) Xerava met the primary endpoint by demonstrating statistical non-inferiority of clinical response compared to ertapenem, a carbapenem and a standard of care treatment for cIAI, and was well-tolerated. We refer to this trial as IGNITE1. In our other pivotal phase 3 clinical trial of Xerava in patients with cIAI, twice-daily IV Xerava met the primary endpoint by demonstrating statistical non-inferiority of clinical response compared to meropenem, another standard of care treatment, and was well-tolerated. We refer to this trial as IGNITE4. In both IGNITE1 and IGNITE4, Xerava achieved high cure rates in patients with poly-microbial infections (Gram-negative, Gram-positive and anaerobic infections), including resistant isolates.

In October 2018, we commenced sales of Xerava in the United States. We are commercializing Xerava in the United States using a small, targeted commercial and medical affairs groups to build and promote access to Xerava. As a result, as of March 1, 2019, we have approximately 40 sales representatives in the field, three strategic market access executives and approximately 10 medical affairs personnel supporting Xerava in the United States.

On September 20, 2018, based on the results of IGNITE1, the European Commission, or EC, granted marketing authorization for Xerava for the treatment of cIAI in adults in all 28 countries of the European Union, or EU, plus Norway, Iceland and Liechtenstein. In February 2018 we entered into a license agreement with Everest Medicines Limited, or Everest Medicines, granting Everest Medicines commercialization rights to eravacycline in China and other Asian territories. In June 2018, Everest Medicines submitted an investigational new drug, or IND, application to the National Medical Products Administration (formerly CHINA FDA) for a phase 3 clinical trial of eravacycline in cIAI. We expect Everest Medicines to begin enrolling patients in this phase 3 clinical trial in the second quarter of 2019.

Subject to obtaining additional financing, we intend to pursue development of Xerava for the treatment of additional indications, including other serious and life-threatening infections. We may pursue these development activities either by ourselves or with collaborators.

We believe that the ability of Xerava to cover MDR Gram-negative bacteria, as well as MDR Gram-positive, anaerobic and atypical bacteria, may enable Xerava to become the drug of choice for first-line empiric treatment of patients with cIAI. Based on in vitro data, Xerava has demonstrated the ability to cover a wide variety of MDR Gram-negative, Gram-positive, anaerobic and atypical bacteria, including multidrug-resistant Klebsiella pneumoniae and multi-drug resistant Acinetobacter. Multidrug-resistant Klebsiella pneumoniae is one of the carbapenem-resistant Enterobacteriaceae (or CREs) listed as an urgent threat and multi-drug resistant Acinetobacter is listed as a serious threat by the Centers for Disease Control and Prevention in a September 2013 report. They are also listed as “Priority 1; Critical Pathogens” in the World Health Organization’s priority pathogens list for R&D, published in February 2017. CREs were a confirmed area of great concern by the World Health Organization in an April 2014 global surveillance report. Gram-negative bacteria that are resistant to multiple available antibiotics are increasingly common and a growing threat to public health.

In addition to Xerava we are also developing other fluorocycline antibiotic compounds, TP-6076 and TP-271, and a tetracycline for the treatment of acute myeloid leukemia, TP-2846. We are developing TP-6076, a fully-synthetic fluorocycline derivative, as a lead candidate under our second-generation program to target unmet medical needs, including MDR Gram-negative bacteria such as carbapenem-resistant Enterobacteriaceae and carbapenem-resistant Acinetobacter baumanii. To date, we have conducted phase 1 single-ascending and multiple-ascending dose studies evaluating the safety, tolerability and pharmacokinetics of IV TP-6076 in healthy volunteers. We are currently conducting a Phase 1 study to assess the bronchopulmonary disposition, pharmacokinetics, and safety of TP-6076 in healthy volunteers. TP-271 is a fully-synthetic fluorocycline that we are developing for respiratory disease caused by bacterial biothreat and antibiotic-resistant public health pathogens, as well as bacterial pathogens associated with community-acquired bacterial pneumonia. To date, we have completed a single- and multiple-ascending dose trials for the IV and oral formulations of TP-271. We expect to report results of these studies at a future scientific meeting. In February 2017, we received Qualified Infectious Disease Product and Fast Track designations from the FDA for TP-271. We do not intend to continue the development of TP-271 unless we secure additional non-dilutive funding for its development. We are also developing TP-2846, a fully-synthetic tetracycline discovered by us, for the treatment of acute myeloid leukemia, or AML. We have recently initiated pre-clinical toxicology studies for this program.

We commenced business operations in July 2006. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital, acquiring and developing our proprietary chemistry technology, identifying potential product candidates, undertaking preclinical studies and clinical trials of our product candidates and initiating commercial sales of Xerava. Prior to October 2018, when we commenced sales of Xerava in the United States, we had not generated any product revenues. For the three months ended December 31, 2018, we generated $0.2 million in net product revenues of Xerava. We have financed our operations primarily through the public offerings and private placements of our equity securities, debt financings, revenue from United States government grants and contract awards and milestone payments from our licensing agreement. As of December 31, 2018, we had received an aggregate of $589.0 million in net proceeds from the issuance of equity securities and borrowings under debt facilities, an aggregate of $57.7 million from government grants and contracts and an aggregate of $9.5 million from licensing agreement milestone payments. As of December 31, 2018, our principal source of liquidity was cash and cash equivalents, which totaled $107.8 million.

As of December 31, 2018, we had an accumulated deficit of $534.0 million. Our net losses were $72.2 million and $114.8 million for the years ended December 31, 2018 and 2017, respectively. We expect that our expenses will decrease in 2019 compared with 2018, as the lower costs associated with the completion of the IGNITE clinical program will offset increased sales, marketing, distribution and outsourced manufacturing expenses related to the launch of Xerava.

We believe that our existing cash and cash equivalents and proceeds from the sales of Xerava will enable us to fund our operating expenses and capital expenditures into the third quarter of 2020. We will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to fund our operations including ongoing spending to commercialize Xerava. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy. Moreover, we will need to generate significant revenue to achieve profitability, and we may never do so. Our failure to generate sufficient cash from operations or to raise additional capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

Financial overview

Product Revenue

Our lead product, Xerava, received approval on August 27, 2018 for the treatment of cIAI in adults. Following FDA approval of Xerava in the United States, we began selling Xerava in October 2018. We sell Xerava to a limited number of specialty distributors in the U.S., who collectively represent our customers. These customers subsequently resell Xerava to hospitals or other treatment centers. In addition to the agreements with these distributors and the related discounts and fees, we are subject to government mandated rebates, chargebacks, and discounts with respect to the purchase of Xerava. Product revenue is recognized net of reserves for all variable consideration, including discounts, chargebacks, government rebates and product returns. For further discussion of our product revenue, see Note 2, Summary of Significant Accounting Policies to the consolidated financial statements.

Collaboration Revenue

In February 2018, we entered into a license agreement with Everest Medicines, whereby we granted Everest Medicines an exclusive license to develop and commercialize eravacycline, for the treatment of cIAI and other indications, in mainland China, Taiwan, Hong Kong, Macau, South Korea and Singapore. Terms of this arrangement include various payment types, including upfront license fees, development, regulatory and commercial milestone payments and payments for clinical supply services. For further discussion of the Everest Medicines collaboration and the related revenue recognition, please see Note 2, Summary of Significant Accounting Policies and Note 3, Significant Agreements and Contracts to the consolidated financial statements.

Government Contract and Grant Revenue

Our contract and grant revenue is derived from funding provided under four awards. These awards include a contract from the Biomedical Advanced Research and Development Authority, or BARDA, an agency of the U.S. Department of Health and Human Services, for the development of Xerava for the treatment of disease caused by bacterial biothreat pathogens, two separate awards from the National Institute of Allergy and Infectious Diseases, or NIAID, a division of the National Institutes of Health, for the development of TP-271. These three awards were made to CUBRC, Inc., or CUBRC, an independent, not-for-profit, research corporation that specializes in United States government-based contracts, with which we are collaborating. CUBRC serves as the prime contractor under these awards, primarily carrying out a program management and administrative role with additional responsibility for the management of preclinical studies. The fourth award is from Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, an international public-private partnership focused on advancing new antimicrobial products to address the threat of antibiotic resistance. For further discussion of our contract and grant revenue agreements and the related revenue recognition, please see Note 2, Summary of Significant Accounting Policies and Note 3, Significant Agreements and Contracts to the consolidated financial statements.

Cost of Revenue

Cost of revenue consists primarily of the manufacturing and distribution costs for Xerava, Xerava net sales-based royalties and the amortization of the intangible asset associated with certain milestones paid to Harvard University related to Xerava. All manufacturing costs incurred prior to Xerava's approval in the United States on August 27, 2018 have been expensed in research and development and are not included in cost of revenue.

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for the research and development of our preclinical and clinical candidates, and include:

- personnel-related expenses, including salaries, benefits and stock-based compensation expense;
- expenses incurred under agreements with contract research organizations, contract manufacturing organizations, and consultants that provide preclinical, clinical, regulatory and manufacturing services;
- certain payments made under our license agreement with Harvard University;
- the cost of acquiring, developing and manufacturing clinical trial materials and lab supplies;
- facility, depreciation and other expenses, which include direct and allocated expenses for rent, maintenance of our facilities, insurance and other supplies; and
- costs associated with preclinical and regulatory activities.

We expense research and development costs to operations as incurred. We recognize costs for certain development activities, such as clinical trials, based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations or information provided to us by our vendors.

We track external development expenses and personnel expense on a program-by-program basis and allocate common expenses, such as scientific consultants and laboratory supplies, to each program based on the personnel resources allocated to such program. Expenses related to facilities, consulting, travel, conferences, stock-based compensation and depreciation are not allocated to a program and are separately classified as other research and development expenses. The following table identifies research and development expenses on a program-specific basis for our product candidates for the years ended December 31, 2018 and 2017:

	Year Ended December 31,	
	2018	2017
	(in thousands)	
Xerava	$31,542	$75,541
BARDA Contract	1,399	5,235
NIAID Contract and NIAID Grant	2,525	3,131
TP-6076	2,092	3,348
CARB-X	2,048	715
Other development programs	3,276	1,186
Other research and development	11,997	12,550
Total research and development	$54,879	$101,706

As of December 31, 2018, we had incurred an aggregate of $287.8 million in research and development expenses related to the development of Xerava, and $37.7 million in research and development expenses related to the development of Xerava that were funded under the BARDA Contract. We expect that our research and development expenses will decrease as we have completed the IGNITE program for Xerava, have determined not to continue development of TP-271 unless we can obtain additional non-dilutive funding, are only in preclinical development for TP-2846 and are only in a phase 1 clinical trial for TP-6076.

Because of the numerous risks and uncertainties associated with product development, however, we cannot determine with certainty the duration and completion costs of current or future clinical trials of our product candidates. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs and timing of clinical trials and development of our product candidates will depend on a variety of factors, including the uncertainties of future clinical and preclinical studies, uncertainties in clinical trial enrollment rate and significant and changing government regulation. In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing capability and commercial viability.

We have licensed our proprietary chemistry technology from Harvard University, or Harvard, on an exclusive worldwide basis under a license agreement that we entered into in August 2006. Under our license agreement, we have paid Harvard an aggregate of $15.8 million in upfront license fees, sublicense fees and development milestone payments. We have also issued 31,379 shares of our common stock to Harvard under the license agreement. We have also agreed to make payments to Harvard upon the achievement of specified future development and regulatory milestones totaling up to $15.1 million for each licensed product candidate ($12.6 million of which has already been paid with respect to Xerava), and to pay tiered royalties in the single digits based on annual worldwide net sales, if any, of licensed products, our affiliates and our sublicensees. We are also obligated to pay Harvard a specified share of non-royalty sublicensing revenues that we receive from sublicensees for the grant of sublicenses under the license and to reimburse Harvard for specified patent prosecution and maintenance costs.

Selling, General and Administrative Expenses

Selling, general and administrative expenses consist principally of personnel-related costs, including salaries and related costs such as benefits and stock-based compensation for personnel in executive, finance, operational, corporate communications, sales, marketing, medical affairs and human resource functions. Other significant selling, general and administrative expenses include marketing and promotion expenses supporting the launch of Xerava, professional fees for legal, patent, auditing and tax services, consulting, and facility costs not otherwise included in research and development expenses.

We anticipate that our selling, general and administrative expenses will increase for a number of reasons, including:

- expansion of infrastructure, including increases in personnel-related costs, consulting, legal, and accounting costs, and directors and officers insurance premiums; and
- increases in our personnel-related and consulting costs as a result of our commercial operations, especially as it relates to the sales and marketing of Xerava.

Interest Income

Interest income consists of interest earned on our cash and cash equivalents. The primary objective of our investment policy is capital preservation.

Interest Expense

Interest expense consists primarily of interest accrued on our outstanding indebtedness and non-cash interest related to the amortization of debt discount costs associated with our term loan facility with Solar Capital. We expect that our interest expense will increase in future periods due to the term loan being outstanding for a longer period, rising interest rates and in the event of additional tranches becoming available to us over the term of the loan.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in our financial statements. On an ongoing basis, we evaluate our estimates and judgments, including product revenue, inventory, estimates related to clinical trial accruals, stock-based compensation expense, contract and grant revenues, and going concern considerations. We base our estimates on historical experience, known trends and events and various other factors that our management believes to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies to be most critical to the judgments and estimates used in the preparation of our financial statements.

Revenue Recognition

Product Revenue

We sell Xerava to a limited number of specialty distributors in the U.S. These customers subsequently resell Xerava to hospitals or other treatment centers. In addition to the agreements with these distributors and the related discounts and fees, we are subject to government mandated rebates, chargebacks, and discounts with respect to the purchase of Xerava.

We recognize Xerava revenue at the time the performance obligation is satisfied, which is the point in time at which the goods are delivered to our customers' facilities, using a transaction price that represents the amount of consideration we expect to receive in exchange for the goods sold. Product revenue is recognized net of reserves for all variable consideration, including discounts, chargebacks, government rebates and product returns.

We evaluate our contracts with customers for all forms of variable consideration which may require an adjustment to the transaction price based on their estimated impact. We estimate variable consideration using the expected value method, which is the sum of probability-weighted amounts in a range of possible outcomes. These outcomes include market events and trends, forecasted product demand patterns, customer buying patterns and statutory requirements. The resulting reserves represent our best estimates of variable consideration we expect to occur.

Revenues from product sales are recorded at the gross sales price, net of reserves for variable consideration, as follows:

- Trade Discounts and Allowances: We offer our customers prompt pay discounts and service fees as stated in our customer contracts. The related reserves are set in the same period the corresponding revenue is recognized, resulting in a reduction of product revenue and receivables or recording of accrued liabilities. We employ the expected value method to estimate the impact of discounts and allowances, subject to any constraints.
- Government Chargebacks and Rebates: Under the terms of our master agreements, Customers may charge us back for reimbursement when they are contractually obligated to sell products to government entities or other end-users at a lower price than the wholesale acquisition cost, or WAC, at which those products were acquired from us. These rebates consist of Medicare, TriCare and Medicaid rebates as well as those related to other government drug pricing and reimbursement programs. We use the expected value method to estimate the variable consideration, subject to any constraints. Chargeback reserves are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue and receivables.

- Product Returns: We estimate the amount of product that may be returned and records this as a reduction in revenue in the relevant period. We currently estimate product return liabilities using available industry data, sales information and visibility into the inventory remaining in the distribution channel. We have not received any returns to date since launch. We use the expected value method to estimate the impact of product returns, subject to any constraints.

Collaboration Revenue Recognition

We entered into an out-licensing agreement that is evaluated under ASC 606, through which we license certain of our product candidates' rights to a third party. Any future out-license agreement entered into by us and additional third parties shall also be evaluated under ASC 606. Terms of these arrangements include various payment types, typically including one or more of the following: upfront license fees; development, regulatory and commercial milestone payments; payments for manufacturing supply services; and/or royalties on net sales of licensed products.

To determine the amount and timing of revenue to be recognized under each agreement, we evaluate the following criteria: (i) confirming the goods or services in the contract; (ii) defining the performance obligations under the agreement; (iii) determining the transaction price, including any constraint on variable consideration; (iv) allocating the transaction price to the performance obligations; and (v) defining how the revenue will be recognized for each performance obligation. In determining the accounting treatment for these arrangements, we develop assumptions to determine the stand-alone selling price for each performance obligation in the contract. These assumptions may include forecasted revenues, development timelines, discount rates and probabilities of technical and regulatory success.

Licenses of Intellectual Property: If the license to our intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize revenue from upfront fees allocated to the license when the license is transferred to the licensee, including any associated know-how and the licensee can use and benefit from the license. For licenses that are bundled with other obligations, we use judgment to evaluate the combined performance obligation to determine whether it is satisfied over time or at a point in time and the appropriate method of measuring completion for purposes of recognizing revenue.

Milestone Payments: For arrangements that include development milestone payments, we evaluate whether the milestones are considered probable and estimate the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the licensee's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received.

Manufacturing Supply: Arrangements that include a promise for future supply of drug substance or drug product for either clinical development or commercial supply at the licensee's discretion are generally considered as options. We assess if these options provide a material right to the licensee and if so, they are accounted for as separate performance obligations. If we are entitled to additional payments when the licensee exercises these options, we recognize revenue when the licensee obtains control of the goods, which is upon delivery.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Government Contract and Grant Revenue

Revenue under our subcontracts under both the NIAID Contract and the BARDA Contract are earned under a cost-plus-fixed-fee arrangement in which we are reimbursed for direct costs incurred plus allowable indirect costs and

a fixed-fee earned. Billings under these contracts are based on approved provisional indirect billing rates, which permit recovery of fringe benefits, allowable overhead and general and administrative expenses and a fixed fee.

Revenue under our subaward under the NIAID Grant and the CARB-X Award are earned under a cost-reimbursable arrangement in which we are reimbursed for direct costs incurred plus allowable indirect costs. Billings under the NIAID Grant and CARB-X Award are based on approved provisional indirect billing rates, which permit recovery of fringe benefits and allowable general and administrative expenses.

We have concluded that our grants are not within the scope of ASC 606, as they do not meet the definition of a contract with a "customer". We have concluded that the grants meet the definition of a contribution and are non-reciprocal transactions. We have further concluded that Subtopic 958-605, Not-for-Profit-Entities-Revenue Recognition also does not apply, as we are a business entity and the grants are with governmental agencies or units. The government grants are technically to a non-profit entity that specializes in government grant administration, project management and oversight (i.e. CUBRC). However, we have concluded that, in effect, it is a grant from the government; as the contracting counterparty CUBRC is merely administering the agreement between the government (which is funding the work) and us (who are performing the work).

In the absence of applicable guidance under GAAP as of January 1, 2018 for the grants, we have developed a policy for the recognition of revenue for the grants as follows:

- Revenue is recognized when the right to payment is realized or is realizable,
- Revenues are realized when services are exchanged for cash or claims to cash. Revenues are not recognized until earned, and
- Our revenue-earning activities involve rendering services that constitute our ongoing major or central operations, and revenues are considered to have been earned when we have substantially accomplished what we must do to be entitled to the benefits represented by the revenues.

We believe this policy is consistent with the overarching premise in ASC 606, to ensure that we recognize revenues to reflect the transfer of promised goods or services to customers in an amount that reflects the consideration to which we expect to be entitled in exchange for those goods or services, even though there is no "exchange" as defined in the ASC. We believe the recognition of revenue as costs are incurred and amounts become earned/realizable is analogous to the concept of transfer of control of a service over time under ASC 606.

Prior to January 1, 2018, we recognized revenue as we performed services under the grants so long as an agreement had been executed and the fees for these services were fixed or determinable, legally billable and reasonably assured of collection. Recognized amounts reflected our partial performance under the grants and equal direct and indirect costs incurred plus fixed fees, where applicable. Revenues and expenses under these arrangements were presented gross. Revenue recognition under this new policy is not materially different than would have been calculated under the old guidance. As a result of adoption of this policy, there was no change to the amounts we have historically recorded to our financial statements.

Accrued Research and Development Expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed for us and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- contract research organizations in connection with the conduct of our clinical trials;
- contract manufacturing organizations with respect to the manufacture of drug supply for clinical trials and manufacture of drug substance and finished product; and
- vendors and consultants in connection with preclinical development activities.

We base our expenses related to clinical studies on our estimates of the services completed and efforts expended pursuant to contracts with multiple contract research organizations that conduct and manage clinical studies on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of subjects and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed, enrollment of subjects, number of sites activated and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, we may report amounts that are too high or too low in any particular period. To date, there have been no material differences from our estimates to the amount actually incurred.

Stock-Based Compensation

We apply the fair value recognition provisions of Financial Accounting Standards Board Accounting Standards Codification Topic 718, Compensation-Stock Compensation, or ASC 718, to account for all stock-based compensation. We recognize compensation costs related to stock options and restricted stock units granted to employees based on the estimated fair value of the awards on the date of grant. Stock compensation related to non-employee awards is remeasured at each reporting period until the awards are vested.

Determining the amount of stock-based compensation to be recorded requires us to develop estimates of the fair value of stock-based awards as of their grant date for awards granted to employees and as of their measurement date for awards granted to non-employees. For awards granted to employees, we recognize stock-based compensation expense ratably over the requisite service period, which in most cases is the vesting period of the award. For awards granted to non-employees, we recognize stock-based compensation expense over the requisite service period using the accelerated attribution method. Calculating the fair value of stock-based awards requires that we make subjective assumptions.

We use the Black-Scholes option pricing model to value our stock option awards. Use of this valuation methodology requires that we make assumptions as to the volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield. Since we completed our IPO on March 25, 2013, we have not had sufficient historical data to support a calculation of volatility and expected life. As such, we have used a weighted-average volatility considering our own volatility and the volatilities of a representative group of publicly traded companies. For purposes of identifying similar entities, we selected a group of publicly traded life science/biotechnology companies based on their disease focus, stage of development, number of compounds in clinical trials and number of years as a publicly-traded company. We use the simplified method as prescribed by the Securities and Exchange Commission Staff Accounting Bulletin No. 107, Share-Based Payment as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term of stock options granted to employees. For non-employee grants, we use an expected term equal to the remaining contractual term of the award. We utilize a dividend yield of zero based on the fact that we have never paid cash dividends and have no current intention of paying cash dividends. The risk-free interest rate used for each grant is based on the U.S. Treasury yield curve in effect at the time of measurement for instruments with a similar expected term.

Results of Operations

Comparison of Years Ended December 31, 2018 and 2017

The following tables summarize the results of our operations for each of the years ended December 31, 2018 and 2017, together with the changes in those items in dollars and as a percentage:

Product Revenue

	Year Ended December 31,		Increase/ (decrease)
	2018	2017	

	(in thousands)		
Revenues:			
Product revenue, net	$178	—	$178
License and collaboration revenue	12,677	—	12,677
Contract revenue	6,049	9,666	(3,617)
Total revenue	18,904	9,666	9,238
Costs and expenses:			
Cost of revenue - product	130	—	130
Cost of revenue - intangible asset amortization	98	—	98
Research and development	54,879	101,706	(46,827)
Selling, general and administrative	37,078	23,675	13,403
Total costs and expenses	92,185	125,381	(33,196)
Loss from operations	(73,281)	(115,715)	42,434
Interest income	1,747	963	784
Interest expense	(624)	—	(624)
Net loss	$(72,158)	$(114,752)	$42,594

We initiated sales of, and therefore realized revenue with respect to, our first commercial product, Xerava, in the United States on October 15, 2018.

License and Collaboration Revenue

In February 2018, we entered into a license agreement with Everest Medicines Limited, whereby we granted Everest Medicines an exclusive license to develop and commercialize eravacycline, for the treatment of cIAI and other indications, in mainland China, and certain surrounding territories. During 2018, we recognized both the $7.0 million upfront payment and the $2.5 million Chinese IND milestone payment as revenue. We also recognized the $3.0 million Phase 3 clinical trial milestone payment as revenue based on the factors described above. In addition, we realized $0.2 million in revenue related to the sale of clinical trial material to Everest Medicines for the planned Chinese clinical trial. These payments were recognized as revenue as we had completed all of our performance obligations.

Revenue from U.S. Government Contracts and Grants

The following table sets forth our contract and grant revenue for the years ended December 31, 2018 and 2017:

	Year Ended December 31,		
Revenue	2018	2017	Increase/ (decrease)
	(in thousands)		
BARDA Contract	$1,457	$5,463	$ (4,006)
NIAID Contract	2,546	3,509	(963)
CARB-X Award	2,046	685	1,361
NIAID Grant	—	9	(9)
	$6,049	$9,666	$ (3,617)

Contract and grant revenue was $6.0 million for the year ended December 31, 2018 compared to $9.7 million for the year ended December 31, 2017, a decrease of $3.6 million, or 37%. This net decrease was due to the scope and timing of activities conducted under our subcontract with respect to the BARDA and NIAID Contracts offset in party by increased activities under the CARB-X Award. Based on the current expected duration of these agreements, we expect government revenue to continue to decline in future periods.

Research and Development Expenses

Research and development expenses were $54.9 million for the year ended December 31, 2018 compared to $101.7 million for the year ended December 31, 2017, a decrease of $46.8 million, or 46%. The decrease was primarily due to lower clinical trial costs associated with conducting our IGNITE program phase 3 clinical trials, which concluded in the first quarter of 2018, and a decrease in chemistry, manufacturing and controls, or CMC, expenses for Xerava.

Selling, General and Administrative Expenses

Selling, general and administrative expenses for the year ended December 31, 2018 were $37.1 million compared to $23.7 million for the year ended December 31, 2017, an increase of $13.4 million, or 57%. This increase was primarily due to an increase in Xerava commercial launch-related expenses and related G&A infrastructure investments.

Interest income

The increase of $0.8 million in interest income for the year ended December 31, 2018 as compared to the year ended December 31, 2017 was driven by improved overall yields on our money market fund investments.

Interest expense

The increase of $0.6 million in interest expense for the year ended December 31, 2018 is related to the Solar debt facility.

Liquidity and Capital Resources

We have incurred losses since our inception and anticipate that we will continue to incur losses for at least the next several years. We expect our total expenses to decrease but remain significant in 2019 and, as a result, we will need additional capital to fund our operations, which we may obtain from additional financings, research funding, collaborations, contract and grant revenue or other sources.

Since our inception, we have funded our operations principally through the receipt of funds from public offerings and private placements of equity securities, debt financings and contract research funding and research grants from the United States government.

As of December 31, 2018, we had cash and cash equivalents of approximately $107.8 million. We invest cash in excess of immediate requirements in accordance with our investment policy, primarily with a view to liquidity and capital preservation. As of December 31, 2018, our funds were held in cash and money market funds.

On January 17, 2017, we entered into a Controlled Equity Offering Sales Agreement, or sales agreement, with Cantor Fitzgerald & Co., as sales agent, or Cantor. On July 7, 2017, we entered into an amendment to the sales agreement, or the amended sales agreement. In accordance with the terms of the sales agreement, we may offer and sell through Cantor, from time to time, shares of our common stock up to an aggregate offering price of $80,000,000 through an "at-the-market" offering program. As of December 31, 2018, we had sold 6,110,446 shares under the amended sales agreement at an average price of $6.49 per share and we had received aggregate cash proceeds of $38.2 million, after deducting the sales commissions and offering expenses. Under the amended sales agreement, Cantor may sell shares of our common stock by methods deemed to be an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, including sales made directly on The Nasdaq Global Select Market or on any other existing trading market for our common stock. We are not obligated to make any sales of shares of our common stock under the amended sales agreement. We or Cantor may suspend or terminate the offering of shares of our common stock upon notice to the other party and subject to other conditions and pay Cantor a commission rate equal to 3.0% of the gross proceeds per share sold.

On August 2, 2017, we sold 10,000,000 shares of common stock in an underwritten public offering at an offering price to the public of $6.50 per share, resulting in net proceeds to us of $60.7 million after deducting underwriting discounts and commissions of $3.9 million and offering costs of $0.4 million. In connection with the offering, we granted the underwriters an option to purchase up to an additional 1,500,000 shares on the same terms and conditions as the offering, pursuant to which the underwriters exercised an option to purchase 107,000 additional shares on August 25, 2017 resulting in additional net proceeds to us of approximately $0.7 million after deducting underwriting discounts and commissions.

On November 2, 2018, we entered into a loan and security agreement with Solar Capital Ltd., as collateral agent and lender, and the other lenders named therein (Solar Capital Ltd. and the other lenders are collectively referred to as the lenders) as more fully described below.

The following table summarizes our sources and uses of cash for each of the periods set forth below:

	Year Ended December 31,	
	2018	2017
	(in thousands)	

Net cash used in operating activities	$(59,628)	$(98,050)
Net cash used in investing activities	(4,954)	(771)
Net cash provided by financing activities	36,447	93,146
Net decrease in cash and cash equivalents	$(28,135)	$(5,675)

During the years ended December 31, 2018 and 2017, our operating activities used net cash of $59.6 million and $98.1 million, respectively. Net cash used by operating activities for the year ended December 31, 2018 improved by $38.4 million compared to the year ended December 31, 2017. The increase is primarily due to an increase in collaboration revenues and a net decrease in operating expenses driven by the trend in research and development expenses.

During the years ended December 31, 2018 and 2017, our investing activities used net cash of $5.0 million and $0.8 million, respectively. The net cash used in investing activities during 2018 was driven by approval milestone payments under our license agreement with Harvard University. 2017 investing activities consisted primary of purchases of property, plant and equipment to facilitate our increased research and development activities and increased headcount.

During the years ended December 31, 2018 and 2017 our net cash provided by financing activities was $36.4 million and $93.1 million, respectively. The net cash provided by financing activities during the year ended December 31, 2018 was primarily due to the Solar debt facility plus sales of common stock under our amended sales agreement with Cantor. The net cash provided by financing activities during the year ended December 31, 2017 consisted primarily of our August 2017 follow-on public offering plus sales under the amended sales agreement with Cantor.

Solar Capital Loan

On November 2, 2018, we entered into a loan and security agreement, which we refer to as the loan agreement with the lenders. The lenders have agreed to make available to us term loans in an aggregate principal amount of up to $75.0 million under the loan agreement. We plan to use the proceeds of the term loans to support the commercial launch of Xerava as well as for working capital and general corporate purposes. The loan agreement provides a term loan commitment of $50.0 million in two potential tranches: (i) a $30.0 million Term A loan facility funded on November 2, 2018 and (ii) a $20.0 million Term B loan facility to be funded at our request no later than October 31, 2020, subject to (A) us having unrestricted net cash proceeds of not less than $50 million from the issuance and sale of common stock and/or from other business activities and (B) us having product revenue greater than or equal to $14.0 million on a six month trailing basis prior to September 30, 2020. Both of these term loans have a maturity date of May 2, 2023. The loan agreement also provides access to an additional Term C loan facility in the amount of $25.0 million, to be funded at the lenders' sole discretion.

Borrowings under all three loan facilities bear interest at a floating per annum rate equal to the 1 Month LIBOR Rate plus 7.25%. We are permitted to make interest-only payments on the initial $30.0 million Term A loan for the fifteen (15) months following the funding date. The interest-only period can be extended by an additional nine (9) months subject to certain conditions being met, including a 12-month trailing revenue milestone of $8.5 million by December 31, 2019; and by an additional six (6) months if we have met certain other conditions, including a 6-month trailing revenue milestone of $14.0 million by September 30, 2020 and raising $50.0 million in new capital. The term of the combined facility will be 54 months, with repayment paid in equal monthly installments commencing at the end of the resulting interest-only period as outlined above through the end of the 54-month term.

We are obligated to pay a final fee equal to 4.00% of the aggregate amount of the term loans funded, to occur upon the earliest of (i) the maturity date, (ii) the acceleration of the term loans, and (iii) the prepayment of the term loans. We have the option to prepay all, but not less than all of the outstanding principal balance of the term loans under the loan agreement. If we prepay all or a portion of the term loans prior to the maturity date, we will pay the lenders a prepayment penalty fee based on a percentage of the outstanding principal balance, equal to 3% if the payment occurs on or before 12 months after the initial funding date, 2% if the prepayment occurs more than 12 months after, but on or before 24 months after, the initial funding date, or 1% if the prepayment occurs more than 24 months after the initial funding date.

In connection with the loan agreement and the funding of the Term A loan facility, we issued to the lenders warrants to purchase an aggregate of 414,365 shares of our common stock, equal to 3.00% of the term loan funded divided by the exercise price of $2.172. We are obligated to issue additional warrants to the lenders in the event the Term B loan facility and/or the Term C loan facility is funded. Those warrants shall also be equal to 3.00% of the term loan funded. The warrants are exercisable at the option of the holder and the exercise price will be the lesser of (a) the 10-day trailing average of our common stock price, as determined as of the close of business day immediately prior to the funding date of the respective term loan, and (b) our common stock price, as determined as of the close of business day immediately prior to the funding date of the respective term loan. Each warrant will terminate 10 years from the date of its original issuance.

Our obligations under the loan agreement are secured by a first priority security interest in substantially all of our assets. The loan agreement contains customary representations, warranties and covenants and also includes customary events of default, including payment defaults, breaches of covenants, change of control and a material adverse change default. We have agreed to maintain cash on hand at all times equal to $10.0 million plus an amount equal to 90 days aged accounts payable subject to certain exceptions.

Upon the occurrence of an event of default, a default interest rate of an additional 4.00% per annum may be applied to the outstanding loan balances, and the lenders may declare all outstanding obligations immediately due and payable and exercise all of their rights and remedies as set forth in the loan agreement and under applicable law.

Operating Capital Requirements

We expect to incur significant operating losses for at least the next several years as we commercialize Xerava and continue development of our other pipeline programs, satisfy our obligations under our license agreement with Harvard and meet our obligations under the loan agreement with the lenders. We may not be able to complete the development of our product candidates if, among other things, our preclinical research and clinical trials with respect to our product candidates are not successful and our manufacturing efforts are not successful,

We believe that our available funds will be sufficient to support our operations into the third quarter of 2020, which we believe will allow us to fund the initial launch of IV Xerava for the treatment of cIAI. We will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to fund our operations including ongoing spending to commercialize Xerava.

We have based our projections of operating capital requirements on assumptions that may prove to be incorrect and we may use all of our available capital resources sooner than we expect. Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical products and the variable nature of the interest-only period and funds accessibility under our debt facility with Solar Capital, we are unable to estimate the exact amount of our operating capital requirements. Our future funding requirements will depend on many factors, including, but not limited to:

- revenues received from commercial sales of Xerava;
- costs of commercialization activities related to the sales and marking of Xerava;
- our ability to access the remaining $45.0 million potentially available to us under the loan agreement;
- the timing and costs of manufacturing activities in connection with the commercialization of Xerava;
- the initiation, progress, timing, costs and results of preclinical studies and clinical trials for our product candidates and potential product candidates;
- the outcome, timing and costs of seeking regulatory approvals;
- the number and characteristics of product candidates that we pursue;
- the costs of commercialization activities for product candidates if we receive marketing approval, including the timing and costs of establishing product sales, marketing, distribution and manufacturing capabilities;
- the terms and timing of any future collaborations, licensing, consulting or other arrangements that we may establish, as we did with Everest Medicines;
    - the amount and timing of any payments we may be required to make, or that we may receive, in connection with the licensing, filing, prosecution, defense and enforcement of any patents or other intellectual property rights, including milestone and royalty payments and patent prosecution fees that we are obligated to pay to Harvard, pursuant to our license agreement;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against intellectual property related claims;
- the extent to which we in-license or acquire other products and technologies; and
- the funding, interest and repayment obligations of our debt facility with Solar Capital.

We expect that we will need to obtain substantial additional funding in order to commercialize Xerava. To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, the ownership interests of our existing stockholders may be materially diluted, and the terms of these securities could include liquidation or other preferences that could adversely affect the rights of our existing stockholders. In addition, additional debt financing, if available, would result in increased fixed payment obligations and may involve agreements that include restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, that could adversely impact our ability to conduct our business. If we are unable to raise capital when needed or on attractive terms, we could be forced to significantly delay, scale back or discontinue the development of our product candidates or commercialization of Xerava, seek collaborators at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available, and relinquish or license, potentially on unfavorable terms, our rights to Xerava or our product candidates that we otherwise would seek to develop or commercialize ourselves.

Contractual Obligations and Commitments

The following table summarizes our outstanding contractual obligations as of payment due date by period at December 31, 2018:

	Payment due by period				
Contractual Obligations	Total	Less than 1 Year	1 -3 Years	3-5 Years	More than 5 Years
	(in thousands)				
Operating leases (1)	$7,379	$1,806	$3,788	$ 1,785	$ —
Long term debt obligation (2)	31,200	—	26,923	4,277	—
Total contractual cash obligations	$38,579	$1,806	$30,711	$ 6,062	$ —

78

(1) On November 29, 2018, we amended our existing operating lease to extend our lease term through November 30, 2022. In third quarter of 2016, we entered into a sublease with respect to a portion of our principal facilities, which consist of office, research and laboratory space located at 480 Arsenal Way, Watertown, Massachusetts, with an unrelated third party. The term of the sublease expires in November 2019, with the sublessee obligated to pay rent to us that approximates the rent we are currently paying to our landlord with respect to such portion of the facility.

(2) The long-term debt obligation is comprised of the outstanding indebtedness under our debt facility with Solar Capital that was executed in November 2, 2018.

We have employment agreements with certain employees which require the funding of a specific level of payments, if certain events, such as a change in control or termination without cause, occur.

In the course of normal business operations, we also have agreements with contract service providers to assist in the performance of our research and development and manufacturing activities. We can elect to discontinue the work under these agreements at any time. We could also enter into additional collaborative research, contract research, manufacturing, and supplier agreements in the future, which may require up-front payments and even long-term commitments of cash.

Off-Balance Sheet Arrangements

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable SEC rules.

ITEM 7A. Quantitative and Qualitative Disclosures About Market Risk

No disclosure required.

ITEM 8. Financial Statements and Supplementary Data

TETRAPHASE PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Tetraphase Pharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Tetraphase Pharmaceuticals, Inc. (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2018, 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 financial position of the Company at December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2018, 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, 2018, 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 March 15, 2019 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.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2007.

Boston, Massachusetts

March 15, 2019

Tetraphase Pharmaceuticals, Inc.

Consolidated Balance Sheets

(In thousands, except par value amounts)

	December 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$107,776	$136,411
Accounts receivable, net	2,274	4,653
Contract asset	3,000	—
Inventory	748	—
Prepaid expenses and other current assets	2,674	6,382
Total current assets	116,472	147,446
Property and equipment, net	1,121	1,395
Restricted cash	699	199
Intangible assets, net	4,652	—
Total assets	$122,944	$149,040
Liabilities and stockholders’ equity		
Current liabilities:		
Accounts payable	$3,210	$5,306
Accrued expenses	11,747	12,559
Deferred revenue	6	660
Total current liabilities	14,963	18,525
Loan payable	28,291	—
Other long term liabilities	8	105
Commitments and contingencies (Note 10)		
Stockholders' equity:		
Preferred stock, par value $0.001 per share; 5,000 shares authorized; no shares issued and outstanding	—	—
Common stock, par value $0.001 per share; 125,000 shares authorized; 53,680 and 51,458 shares issued and outstanding at December 31, 2018 and 2017, respectively	53	51
Additional paid-in capital	613,671	592,243
Accumulated deficit	(534,042)	(461,884)
Total stockholders’ equity	79,682	130,410
Total liabilities and stockholders’ equity	$122,944	$149,040

See accompanying notes to consolidated financial statements.

82

Tetraphase Pharmaceuticals, Inc.

Consolidated Statements of Operations and Comprehensive Loss

(In thousands, except per share data)

	Years Ended December 31,	
	2018	2017
Revenues:		
Product revenues, net	$178	$—
License and collaboration revenue	12,677	—
Government revenue	6,049	9,666
Total revenue	18,904	9,666
Expenses:		
Cost of revenue - product	130	—
Cost of revenue - intangible asset amortization	98	—
Research and development	54,879	101,706
Selling, general and administrative	37,078	23,675
Total expenses	92,185	125,381
Loss from operations	(73,281)	(115,715)
Other income and expenses		
Interest income	1,747	963
Interest expense	(624)	—
Net loss	$(72,158)	$(114,752)
Net loss per share-basic and diluted	$(1.37)	$(2.63)
Weighted-average common shares used in net loss per share-basic and diluted	52,514	43,582
Comprehensive loss	$(72,158)	$(114,752)

See accompanying notes to consolidated financial statements.

Tetraphase Pharmaceuticals, Inc.

Consolidated Statements of Stockholders' Equity

(In thousands)

	Common Shares	Shares Amount	Additional Paid-In Capital	Accumulated Deficit	Total Stockholders' Equity (Deficit)
Balance at December 31, 2016	36,942	$ 37	$ 487,148	$ (347,132)	$ 140,053
Issuance of common stock under stock plans	173	—	289	—	289
Issuance of common stock from follow-on public offering less underwriters discounts and issuance costs	10,107	10	61,384	—	61,394
Issuance of common stock under "at-the-market" equity offering sales agreement, less issuance costs	4,158	4	31,138	—	31,142
Issuance of common stock under employee stock purchase plan	78	—	321	—	321
Stock-based compensation expense	—	—	11,963	—	11,963
Net loss	—	—	—	(114,752)	(114,752)
Balance at December 31, 2017	51,458	$ 51	$ 592,243	$ (461,884)	$ 130,410
Issuance of common stock under stock plans	184	—	271	—	271
Issuance of common stock under "at-the-market" equity offering sales agreement, less issuance costs	1,952	2	7,037	—	7,039
Issuance of warrants to purchase common stock	—	—	803	—	803
Issuance of common stock under employee stock purchase plan	86	—	188	—	188
Stock-based compensation expense	—	—	13,129	—	13,129
Net loss	—	—	—	(72,158)	(72,158)
Balance at December 31, 2018	53,680	$ 53	$ 613,671	$ (534,042)	$ 79,682

See accompanying notes to consolidated financial statements.

Tetraphase Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows

(In thousands)

	Years Ended December 31,	
	2018	2017
Operating activities		
Net loss	$(72,158)	$(114,752)
Adjustments to reconcile net loss to net cash used in operating activities		
Depreciation and amortization	576	431
Non-cash interest expense related to notes payable	145	—
Stock-based compensation expense	13,129	11,963
Changes in operating assets and liabilities:		
Accounts receivable	2,379	(2,864)
Contract asset	(3,000)	—
Inventory	(748)	—
Prepaid expenses and other assets	3,708	200
Accounts payable	(2,096)	2,751
Accrued expenses and other liabilities	(909)	4,816
Deferred revenue	(654)	(595)
Net cash used in operating activities	(59,628)	(98,050)
Investing activities		
Acquisition of intangible assets	(4,750)	—
Purchases of property and equipment	(204)	(771)
Net cash used in investing activities	(4,954)	(771)
Financing activities		
Proceeds from sale of common stock, net of issuance costs	7,039	92,536
Proceeds from issuance of debt, net of issuance costs	28,949	—
Proceeds from issuance of stock under stock plans	459	610
Net cash provided by financing activities	36,447	93,146
Net increase (decrease) in cash, cash equivalents and restricted cash	(28,135)	(5,675)
Cash, cash equivalents and restricted cash at beginning of period	136,610	142,285
Cash, cash equivalents and restricted cash at end of period	$108,475	$136,610
Supplemental cash flow information		
Cash paid for interest	$480	$—

See accompanying notes to consolidated financial statements.

Tetraphase Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements

(1) Organization and Operations

The Company

Tetraphase Pharmaceuticals, Inc. (the "Company") is a biopharmaceutical company using its proprietary chemistry technology to create, develop and commercialize novel tetracyclines for serious and life-threatening conditions, including bacterial infections caused by multidrug-resistant, or MDR, bacteria. The Company developed its lead product candidate, Xerava™ (eravacycline), a fully synthetic fluorocycline, as an intravenous, or IV antibiotic for use as a first-line empiric monotherapy for the treatment of MDR infections, including MDR Gram-negative infections, such as those found in complicated intra-abdominal infections, or cIAI.

On August 27, 2018, the United States Food and Drug Administration, or FDA, approved Xerava for the treatment of cIAI in adults. Approval of Xerava was based on its IGNITE (Investigating Gram-Negative Infections Treated with Eravacycline) phase 3 program. In October 2018, the Company commenced sales of Xerava in the United States.

On September 20, 2018, based on the results of IGNITE1, the European Commission, or EC, granted marketing authorization for Xerava for the treatment of cIAI in adults in all 28 countries of the European Union, or EU, plus Norway, Iceland and Liechtenstein.

In addition to Xerava, the Company is pursuing development of TP-6076, a fully synthetic fluorocycline, targeted at unmet medical needs, including multidrug-resistant Gram-negative bacteria, and TP-271, a fully synthetic fluorocycline being developed for respiratory disease caused by bacterial biothreat pathogens and. Both of these programs are in phase 1. The Company is no longer developing eravacycline (IV or oral formulations) for the treatment of complicated urinary tract infections as a result of the clinical outcomes of IGNITE2 and IGNITE3. The Company does not intend to continue the development of TP-271 unless it secures additional non-dilutive funding for its development. The Company is also pursuing development of TP-2846, a tetracycline for the treatment of acute myeloid leukemia.

The Company has incurred annual net operating losses in every year since its inception. As of December 31, 2018, the Company had incurred losses since inception of $534.0 million. The Company has financed its operations primarily through the public offerings and private placements of equity securities, debt financings, revenue from United States government grants and contract awards and milestone payments from its licensing agreement. The Company will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources to fund our operations including ongoing spending to commercialize Xerava.

There can be no assurance that the Company will be able to obtain additional debt or equity financing or generate product revenue or revenues from collaborative partners, on terms acceptable to the Company, on a timely basis or at all. The failure of the Company to obtain sufficient funds on acceptable terms when needed could have a material adverse effect on the Company's business, results of operations and financial condition.

(2) Summary of Significant Accounting Policies

Segment Information

Operating segments are defined as components of an enterprise about which separate discrete information is available for evaluation by the chief operating decision maker, or decision-making group, in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business in one operating segment, which is the business of developing and commercializing its proprietary chemistry technology to create novel antibiotics for serious and life-threatening infections, including multidrug-resistant infections.

Use of Estimates

The preparation of financial statements in conformity with generally accepted accounting principles (”GAAP”) requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, revenue and expenses, and related disclosures. On an ongoing basis, the Company’s management evaluates its estimates, including product revenue, inventory, estimates related to clinical trial accruals, stock-based compensation expense, contract and grant revenues, and going concern considerations. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. Actual results may differ from those estimates or assumptions.

Concentrations of Credit Risk and Off-Balance Sheet Risk

Financial instruments that potentially subject the Company to concentrations of credit risk are primarily cash, cash equivalents and restricted cash. The Company maintains its cash and cash equivalent balances in the form of cash and money market accounts with financial institutions that management believes are creditworthy. The Company's investment policy includes guidelines on the quality of the institutions and financial instruments and defines allowable investments that the Company believes minimize its exposure to concentration of credit risk. The Company has no financial instruments with off-balance-sheet risk of loss.

The Company is also subject to credit risk on its accounts receivable, including from its trade customer receivables and contract receivables from CUBRC Inc. ("CUBRC"), an independent, not-for-profit, research corporation that specializes in U.S. government-based contracts, and the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, an international public-private partnership focused on advancing new antimicrobial products to address the threat of antibiotic resistance. The company has a strong track record of collection on its accounts receivable from both CUBRC and CARB-X.

The Company's trade receivables from product sales have payment terms ranging from 30 to 60 days. The Company has evaluated the creditworthiness of its customers and has determined each of them to be creditworthy. The Company has not experienced any trade receivable losses to date.

Principles of Consolidation

The consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. All significant intercompany balances and transactions have been eliminated in consolidation.

Cash and Cash Equivalents

The Company considers all highly liquid investments with maturities of three months or less from the date of purchase to be cash equivalents. Cash and cash equivalents at December 31, 2018 and 2017 consisted of cash and money market funds.

Fair Value Measurements

The Company's financial instruments consist principally of cash and cash equivalents, accounts receivable, accounts payable, and accrued liabilities. Fair value measurements are classified and disclosed in one of the following three categories:

Level 1 — Quoted prices in active markets for identical assets or liabilities.

Level 2 — Inputs other than Level 1 that are observable, either directly or indirectly, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3 — Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

Financial instruments measured at fair value as of December 31, 2018 and 2017 are classified below based on the three fair value hierarchy tiers described above (in thousands):

		Fair Value Measurements at Reporting Date Using		
	Balance	Level 1	Level 2	Level 3
December 31, 2018				
Cash and money market funds	$107,776	$107,776	$ —	$ —
December 31, 2017				
Cash and money market funds	$136,411	$136,411	$ —	$ —

The Company measures cash equivalents at fair value on a recurring basis. The fair value of cash equivalents is determined based on “Level 1” inputs, which consist of quoted prices in active markets for identical assets.

Accounts Receivable

Accounts receivable at December 31, 2018 and 2017 represent amounts due from two main sources: (1) Trade accounts receivable of $0.1 million consisting of payments to be received from customers for sales of Xerava, net of prompt payment discounts, chargebacks, rebates and certain fees and (2) contract accounts receivable of $2.2 million related to the Company’s government-related agreements.

Contract accounts receivable relate to payments from entities administering the Company's government-related agreements which include unbilled contract accounts receivable of $0.7 million and $2.4 million at December 31, 2018 and 2017, respectively.

Contract Balances

The Company recognizes a contract asset when the Company transfers goods or services to a customer before the customer pays consideration or before payment is due, excluding any amounts presented as a receivable (i.e. accounts receivable). A contract asset represents the Company's right to consideration in exchange for goods or services that the Company has transferred to a customer.

As of December 31, 2018, such contract assets were $3.0 million in relation to milestone payments to be received under the terms of the Everest Medicines License Agreement. For the twelve-month period ended December 31, 2018, the Company recognized license revenue included in such contract assets of $3.0 million. See Note 3 for further details.

Inventory

Inventory is stated at the lower of cost or net realizable value on a first-in, first-out (FIFO) basis. Prior to the regulatory approval of Xerava, given the uncertainty of approval, the Company recognized as research and development expense costs related to the manufacture of Xerava. Upon approval of Xerava, the Company began to capitalize such costs as inventory.

During each quarter, the Company performs an assessment quantifying any potential excess or obsolete inventory and writes down any such inventory to its net realizable value in the period in which the impairment is identified. These adjustments are based upon multiple factors, including inventory levels at the company and at its specialty distributors, projected demand and product shelf life. These impairment charges, if required, are recorded as a cost of revenue. As of December 31, 2018, estimates of excess inventory were immaterial.

Property and Equipment, Net

Property and equipment are stated at cost, less accumulated depreciation and amortization. Depreciation and amortization are recognized using the straight-line method over the estimated useful lives of the respective assets, which is generally three to five years. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful economic lives of the related assets.

Restricted Cash

At December 31, 2018 the Company had $699,000 in restricted cash deposits with a bank, of which $500,000 is serving as security for our field force corporate credit card program. $159,000 is collateral for a letter of credit issued to the landlord of the Company's leased facility. If the Company defaults on its rental obligations, $159,000 will be payable to the landlord. In addition, the Company has $40,000 in restricted cash to secure the Company's corporate purchasing credit card issued through the same bank.

Intangible Assets

The Company maintains definite-lived intangible assets related to certain capitalized milestone payments to Harvard University (Harvard). These assets are amortized over their remaining useful lives, which are estimated based on the shorter of the remaining patent life or the estimated useful life of the underlying product. Intangible assets are

amortized using the economic consumption method if anticipated future revenues can be reasonably estimated. The straight-line method is used when future revenues cannot be reasonably estimated.

The Company assesses its intangible assets for impairment if indicators are present or changes in circumstance suggest that impairment may exist. Events that could result in an impairment, or trigger an interim impairment assessment, include the receipt of additional clinical or nonclinical data regarding one of the Company's drug candidates or a potentially competitive drug candidate, changes in the clinical development program for a drug candidate, or new information regarding potential sales for the drug. If impairment indicators are present or changes in circumstance suggest that impairment may exist, the Company performs a recoverability test by comparing the sum of the estimated undiscounted cash flows of each intangible asset to its carrying value on the consolidated balance sheet. If the undiscounted cash flows used in the recoverability test are less than the carrying value, the Company would determine the fair value of the intangible asset and recognize an impairment loss if the carrying value of the intangible asset exceeds its fair value.

The Company capitalized milestone payments of $4.75 million related to regulatory approval of Xerava in the US and EU, which will be amortized over their estimated useful lives of approximately 12 years. Amortization expense for each of the following five years is expected to be $0.4 million.

Revenue Recognition

Product Revenue

Revenue recognition under ASC 606 is applied through a five-step model as follows: (1) identify the contract(s) with the customer; (2) identify performance obligations in the contract; (3) determine the transaction price; (4) allocate transaction price to the performance obligation; and (5) recognize revenue when (or as) each performance obligation is satisfied.

The Company's arrangements with its distributors are determined to be contracts within the scope of ASC 606 when all five criteria in ASC 606 are met. These five criteria were assessed at the inception of each arrangement. Since the criteria were met during this initial assessment, the Company will not reassess the criteria unless there is an indication of a significant change in facts and circumstances. In order to meet the definition of a contract, it must also be probable that the Company will collect the consideration to which it is entitled for goods or services to be transferred. Once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services to be delivered with each contract, determines whether those are performance obligations and the related transaction price. The Company then recognizes revenue based on the transaction price that is allocated to the respective performance obligation when the performance obligation is satisfied.

The Company's product revenue consists of the sales of Xerava, which the Company began selling to customers in October 2018. The Company sells Xerava to specialty distributors. These customers resell Xerava to hospitals or other treatment centers. In addition to these distributor agreements and the related discounts and allowances, the Company is subject to government mandated rebates, chargebacks, and discounts with respect to the purchase of the Company's product. Product revenue is recognized net of reserves for all variable consideration, including discounts, chargebacks, government rebates and product returns. The Company is expensing the costs of obtaining and fulfilling these contracts when incurred. The Company has opted to immediately expense the incremental cost of obtaining a contract when the underlying related asset would have been amortized over one year or less.

Reserves for Variable Consideration

The Company evaluates its contracts with customers for forms of variable consideration which may require an adjustment to the transaction price based on their estimated impact. Revenues from product sales are recorded at the gross sales price, net of variable consideration, as described above.

The Company estimates variable consideration using the expected value method, which is the sum of probability-weighted amounts in a range of possible outcomes. These outcomes include market events and trends, forecasted product demand patterns, customer buying patterns and statutory requirements. The resulting reserves represent the Company's best estimates of variable consideration it expects to occur.

Before it can include an amount of variable consideration in the transaction price, the Company must consider whether the amount of variable consideration is constrained. The Company includes estimates of variable consideration in revenue only when it has a "high degree of confidence" that revenue will not be reversed in a subsequent reporting period. To include variable consideration in the estimated transaction price, the entity has to

conclude that it is “probable” that a significant revenue reversal will not occur in future periods, considering both the likelihood and magnitude of a revenue reversal to apply the constraint. Based on the above, the Company applies the constraint to variable consideration included in its contracts if it cannot conclude that it is probable that a significant revenue reversal will not occur in future periods.

Trade Discounts and Allowances: The Company offers its customers prompt pay discounts and service fees as stated in its customer contracts. The Company pays these service fees to its customers in exchange for their performance of various product distribution, marketing and promotional services targeted at advancing end-user sales of the Company’s product. The related reserves are set in the same period the corresponding revenue is recognized, resulting in a reduction of product revenue.

Government Chargebacks and Rebates: Under the terms of the Company's master agreements, customers may charge back the Company for reimbursement when they are contractually obligated to sell products to government entities or other end-users at a lower price than the wholesale acquisition cost, or WAC, at which those products were acquired from the Company. These rebates consist of Medicare, TriCare and Medicaid rebates as well as those related to other government drug pricing and reimbursement programs.

Product Returns: Products are eligible for return by the Customers in various scenarios under the Company's returns policies included as part of its master distribution agreements. Return options are provided for expired merchandise, short-dated merchandise, products damaged in transit, or any discontinued, withdrawn, or recalled products. The Company estimates the amount of product that may be returned and records this as a reduction in revenue in the relevant period. The Company currently estimates product return liabilities using available industry data, sales information and visibility into the inventory remaining in the distribution channel. The Company has not received any returns to date since launch.

The Company will continue to assess its estimates of the various components of variable consideration as it accumulates additional historical data and make adjustments to these estimates and allowances accordingly.

Collaboration Revenue

The Company has entered into an out-licensing agreement that is evaluated under Accounting Standards Codification, Topic 606 ("Topic 606"), Revenue from Contracts with Customers, through which the Company licenses certain of its product candidates' rights to a third party. Any future out-licensing agreements entered into by the Company and additional third parties shall also be evaluated under Topic 606. Terms of these arrangements include various payment types, typically including one or more of the following: upfront license fees; development, regulatory and commercial milestone payments; payments for manufacturing supply services; and/or royalties on net sales of licensed products.

To determine the amount and timing of revenue to be recognized under each agreement, the Company evaluates the following criteria: (i) confirming the goods or services in the contract; (ii) defining the performance obligations under the agreement; (iii) determining the transaction price, including any constraint on variable consideration; (iv) allocating the transaction price to the performance obligations; and (v) defining how the revenue will be recognized for each performance obligation. In determining the accounting treatment for these arrangements, the Company develops assumptions to determine the stand-alone selling price for each performance obligation in the contract. These assumptions may include forecasted revenues, development timelines, discount rates and probabilities of technical and regulatory success.

Licenses of Intellectual Property: If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes revenue from upfront fees allocated to the license when the license, including any associated know-how, is transferred to the licensee and the licensee can use and benefit from the license. For licenses that are bundled with other obligations, the Company uses judgment to evaluate the combined performance obligation to determine whether it is satisfied over time or at a point in time and the appropriate method of measuring completion for purposes of recognizing revenue.

Milestone Payments: For arrangements that include development milestone payments, the Company evaluates whether the milestones are considered probable and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received.

Manufacturing Supply: Arrangements that include a promise for future supply of drug substance or drug product for either clinical development or commercial supply at the licensee's discretion are generally considered as options. The Company assesses if these options provide a material right to the licensee and if so, they are accounted for as separate performance obligations. If the Company is entitled to additional payments when the licensee exercises these options, the Company recognizes revenue when the licensee obtains control of the goods, which is upon delivery.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Government Contract Revenue

The Company's government contract revenue has been derived from its subcontracts with CUBRC under the BARDA Contract, and the NIAID Contract, its subaward under the NIAID Grant and its cost reimbursement Sub-Award Agreement with the Trustees of Boston University, the administrator of the CARB-X program (Note 3). The Company recognizes revenue under these best-efforts, cost-reimbursable and cost-plus-fixed-fee subcontracts and subaward as the Company performs services under the subcontracts and subaward so long as a subcontract and subaward has been executed and the fees for these services are fixed or determinable, legally billable and reasonably assured of collection. Recognized amounts reflect the Company's partial performance under the subcontracts and subaward and equal direct and indirect costs incurred plus fixed fees, where applicable. The Company does not recognize revenue under these arrangements for amounts related to contract periods where funding is not yet committed as amounts above committed funding thresholds would not be considered fixed or determinable or reasonably assured of collection. Revenues and expenses under these arrangements are presented gross on the consolidated statements of operations and comprehensive loss as the Company has determined it is the primary obligor under these arrangements relative to the research and development services it performs as lead technical expert.

Revenue under the Company's subcontracts under both the NIAID Contract and the BARDA Contract and under the CARB-X Award are earned under a cost-plus-fixed-fee arrangement in which the Company is reimbursed for direct costs incurred plus allowable indirect costs and a fixed-fee earned. Billings under these arrangements are based on approved provisional indirect billing rates, which permit recovery of allowable fringe benefits, allowable overhead and general and administrative expenses and a fixed fee.

Revenue under the Company's subaward under the NIAID Grant was earned under a cost-reimbursable arrangement in which the Company was reimbursed for direct costs incurred plus allowable indirect costs. Billings under the NIAID Grant are based on approved provisional indirect billing rates, which permit recovery of fringe benefits and allowable general and administrative expenses.

Cost of Revenue

Cost of revenue consists primarily of the manufacturing and distribution costs for Xerava, Xerava net sales-based royalties and the amortization of the intangible asset associated with certain milestones paid to Harvard related to Xerava. All manufacturing costs incurred prior to Xerava's approval in the United States on August 27, 2018 have been expensed in research and development and are not included in cost of revenue.

Research and Development Expenses

Research and development costs are charged to expense as incurred and include, but are not limited to:

- personnel-related expenses, including salaries, benefits, and stock-based compensation expense;
- expenses incurred under agreements with contract research organizations, contract manufacturing organizations and consultants that provide preclinical, clinical, regulatory and manufacturing services;
- certain payments made under the Company's license agreement with Harvard University;
- the cost of acquiring, developing and manufacturing clinical trial materials and lab supplies;
- facility, depreciation and other expenses, which include direct and allocated expenses for rent, maintenance of the Company's facilities, insurance and other supplies; and
- costs associated with preclinical and regulatory.

Costs for certain development activities, such as clinical trials, are recognized based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations, or information provided

to the Company by its vendors on their actual costs incurred. Payments for these activities are based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the financial statements as prepaid or accrued research and development. In certain circumstances, the Company is required to make nonrefundable advance payments to vendors for goods or services that will be received in the future for use in research and development activities. In such circumstances, the nonrefundable advance payments are deferred and capitalized, even when there is no alternative future use for the research and development, until related goods or services are provided.

Comprehensive Loss

Comprehensive loss consists of net income or loss and changes in equity during a period from transactions and other events and circumstances generated from non-owner sources. The Company's net loss equals comprehensive loss for all periods presented.

Income Taxes

The Company uses the liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial reporting and the tax reporting basis of assets and liabilities and are measured using the enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. The Company provides a valuation allowance against net deferred tax assets unless, based upon the available evidence, it is more likely than not that the deferred tax assets will be realized. The Company has evaluated available evidence and concluded that the Company may not realize the benefit of its deferred tax assets; therefore a valuation allowance has been established for the full amount of the deferred tax assets. The Company's practice is to recognize interest and/or penalties related to income tax matters in income tax expense.

The Tax Cuts and Jobs Act ("the Act") was enacted on December 22, 2017. The Act reduces the US federal corporate tax rate from 34% to 21%, requires companies to pay a one-time transition tax on earnings of certain foreign subsidiaries that were previously tax deferred and creates new taxes on certain foreign sourced earnings. On December 22, 2017, the Securities and Exchange Commission issued guidance under Staff Accounting Bulletin No. 118, Income Tax Accounting Implications of the Tax Cuts and Jobs Act ("SAB 118") directing taxpayers to consider the impact of the U.S. legislation as "provisional" when it does not have the necessary information available, prepared or analyzed (including computations) in reasonable detail to complete its accounting for the change in tax law.

At December 31, 2018, the accounting for the tax effects of enactment of the Act was completed and did not recognize any material adjustments from the provisional amounts that were recorded.

Stock-Based Compensation

The Company determines stock-based compensation at the grant date using the Black-Scholes option pricing model to estimate fair value for employee equity awards. The Company recognizes the value of the award as an expense on a straight-line basis over the requisite service period using the estimated fair market value of the stock and accounts for forfeitures as they occur. For employee awards with performance conditions, the Company assesses whether the condition is probable of achievement, in which case, the fair value of the award is recognized over the requisite service period. The Company records stock-based compensation expense for payments issued to non-employees based on the fair value of the awards using the Black-Scholes option pricing model. Stock-based compensation payments issued to non-employees are revalued at each reporting period and as the equity instruments vest and are recognized as expense using the accelerated attribution method over the related service period.

Going Concern Assessment

Accounting Standards Update ("ASU") No. 2014-15, Presentation of Financial Statements - Going Concern, requires management to evaluate the company's ability to continue as a going concern one year beyond the filing date of the given financial statements. This evaluation requires management to perform two steps. First, management must evaluate whether there are conditions and events that raise substantial doubt about the entity's ability to continue as a going concern. Second, if management concludes that substantial doubt is raised, management is required to consider whether it has plans in place to alleviate that doubt. Disclosures in the notes to the financial statements are required if management concludes that substantial doubt exists or that its plans alleviate the substantial doubt that was raised.

Based on a detailed cash forecast incorporating Xerava commercialization activities, selective development of its pipeline candidates and related spending plans, the Company expects its cash to last more than one year beyond the date that the financial statements were issued. Management's belief with respect to its ability to fund operations is based on estimates that are subject to risks and uncertainties. If actual results are different from management's estimates, the Company may need to seek additional funding sooner than anticipated. Based on this analysis, no additional disclosures were required.

Recently Adopted Accounting Pronouncements

In November 2016, the Financial Accounting Standard Board (FASB) issued Accounting Standards Update No. 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash (ASU 2016-18), which requires companies to include amounts generally described as restricted cash and restricted cash equivalents in cash and cash equivalents when reconciling beginning-of-period and end-of-period total amounts shown on the statements of cash flows. The Company adopted the new standard effective January 1, 2018, using the retrospective transition approach. The reclassified restricted cash balances from operating activities to changes in cash, cash equivalents and restricted cash on the condensed consolidated statements of cash flows were not material for all periods presented.

In May 2014, the FASB issued ASU No. 2014-09, Revenue from Contracts with Customers (Topic 606), which supersedes all existing revenue recognition requirements, including most industry-specific guidance. The new standard requires a company to recognize revenue when it transfers goods or services to customers in an amount that reflects the consideration that the company expects to receive for those goods or services. In August 2015, the FASB issued ASU No. 2015-14, Revenue from Contracts with Customers (Topic 606): Deferral of the Effective Date, which delayed the effective date of the new standard from January 1, 2017 to January 1, 2018. The FASB also agreed to allow entities to choose to adopt the standard as of the original effective date. The FASB has subsequently issued ASU 2016-08, Revenue from Contracts with Customers (Topic 606): Principal versus Agent Considerations (Reporting Revenue Gross versus Net); ASU 2016-10, Revenue from Contracts with Customers (Topic 606): Identifying Performance Obligations and Licensing; ASU 2016-12, Revenue from Contracts with Customers (Topic 606): Narrow-Scope Improvements and Practical Expedients; and ASU 2016-20, Technical Corrections and Improvements to Topic 606, Revenue from Contracts with Customers. The Company adopted this standard retrospectively to all periods presented.

In addition to its evaluation of its product and collaboration revenue under Topic 606 as discussed above, the Company has concluded that its government grants are not within the scope of Topic 606, as they do not meet the definition of a contract with a “customer”. The Company has concluded that the grants meet the definition of a contribution and are non-reciprocal transactions. The Company has further concluded that Subtopic 958-605, Not-for-Profit-Entities-Revenue Recognition also does not apply, as the Company is a business entity and the grants are with governmental agencies or units. The government grant is technically to a non-profit entity that specializes in government grant administration, project management and oversight (i.e. CUBRC). However, the Company has concluded that, in effect, it is a grant from the government; as the contracting counterparty CUBRC is merely administering the agreement between the government (who is funding the work) and the Company (who is performing the work).

In the absence of applicable guidance under GAAP as of January 1, 2018 for the grants, the Company has developed a policy for the recognition of revenue for the grants as follows:

- Revenue is recognized when the right to payment is realized or is realizable
- Revenues are realized when services are exchanged for cash or claims to cash. Revenues are not recognized until earned.
- The Company’s revenue-earning activities involve rendering services that constitute its ongoing major or central operations, and revenues are considered to have been earned when the Company has substantially accomplished what it must do to be entitled to the benefits represented by the revenues.

The Company believes this policy is consistent with the overarching premise in Topic 606, to ensure that it recognizes revenues to reflect the transfer of promised goods or services to customers in an amount that reflects the consideration to which it expects to be entitled in exchange for those goods or services, even though there is no “exchange” as defined in the ASC. The Company believes the recognition of revenue as costs are incurred and amounts become earned/realizable is analogous to the concept of transfer of control of a service over time under ASC 606.

Prior to January 1, 2018, the Company recognized revenue as it performed services under the grants so long as an agreement had been executed and the fees for these services were fixed or determinable, legally billable and reasonably assured of collection. Recognized amounts reflected the Company's partial performance under the grants and equal direct and indirect costs incurred plus fixed fees, where applicable. Revenues and expenses under these arrangements were presented gross. Revenue recognition under this new policy is not materially different than would have been calculated under the old guidance. As a result of the adoption of this policy, there was no change to the amounts the Company has historically recorded to its financial statements.

There have been no other significant changes to the Company's significant accounting policies since the beginning of this fiscal year.

Recent Accounting Pronouncements Not Yet Adopted

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842). The new standard requires that all lessees recognize the assets and liabilities that arise from leases on the balance sheet and disclose qualitative and quantitative information about its leasing arrangements. The new standard will be effective for the Company on January 1, 2019. The FASB subsequently issued the following amendments to ASU 2016-02, which have the same effective date and transition date of January 1, 2019: ASU No. 2018-10, Codification Improvements to Topic 842, Leases, which amends certain narrow aspects of the guidance issued in ASU 2016-02 and ASU No. 2018-11, Leases (Topic 842): Targeted Improvements, which allows for a transition approach to 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 as well as an additional practical expedient for lessors to not separate non-lease components from the associated lease component.

The Company intends to adopt the standard at the effective date of January 1, 2019 by applying the new lease requirements beginning on the effective date without restating prior periods. Upon adoption, the Company plans to elect the package of practical expedients permitted under the transition guidance which, among other things, allows the Company to carry forward historical classification of its existing leases. While the Company is continuing to evaluate the impact of adopting the standard and its related amendments, the Company expects that the standard will result in recognition of material right-of-use assets and lease liabilities on the Company’s consolidated balance sheet. The Company is currently implementing controls and processes to address the future financial presentation and disclosure requirements of the standard.

Subsequent Events

The Company has considered all events occurring subsequent to December 31, 2018 and has concluded that all significant events have been disclosed in the financial statements and accompanying notes.

Net Loss per Common Share

Basic net loss per share is calculated by dividing the net loss by the weighted average number of shares of Common Stock outstanding for the period, without consideration for common stock equivalents. Diluted net loss per share is computed by dividing the net loss by the weighted average number of common share equivalents outstanding for the period determined using the treasury-stock method. For purposes of this calculation, warrants, stock options, and restricted stock units are considered to be common stock equivalents and are only included in the calculation of diluted net loss per share when their effect is dilutive.

The amounts in the table below were excluded from the calculation of diluted weighted-average shares outstanding, prior to the use of the treasury stock method, due to their anti-dilutive effect:

	Year Ended December 31,	
	2018	2017
Warrants	414,365	—

Outstanding stock options	7,322,436	5,997,794
Unvested restricted stock units	1,080,440	282,034
Total	8,817,241	6,279,828

(3) Significant Agreements and Contracts

License Agreement

In August 2006, the Company entered into a license agreement for certain intellectual property with Harvard University. Under the license agreement, as of December 31, 2018, the Company has paid Harvard an aggregate of $15.8 million in upfront license fees, sublicense fees and development milestone payments for the licensed Harvard technology, and has issued 31,379 shares of common stock to Harvard.

For each product covered by the license agreement, the Company is obligated to make certain payments totaling up to approximately $15.1 million upon achievement of certain development and regulatory milestones and to pay additional royalties on net sales of such product. In January 2007 and April 2010, the Company and the University amended the license agreement to include certain additional intellectual property. The Company paid an additional $25,000 to the University with each amendment. In February 2011, the license agreement was further amended to include additional intellectual property in the license granted by the University without the payment of any additional consideration. The license agreement was further amended in December 2017 to change certain

payments due to Harvard. For the years ended December 31, 2018 and 2017, the company paid Harvard $7.8 million and $1.8 million, respectively, in regulatory milestone payments.

Other Material Agreements

Everest Medicines License Agreement

In February 2018, the Company entered into a license agreement (the "Everest License Agreement") with Everest Medicines Limited ("Everest Medicines"), whereby the Company granted Everest Medicines an exclusive license to develop and commercialize eravacycline, for the treatment of complicated intra-abdominal infections and other indications, in mainland China, Taiwan, Hong Kong, Macau, South Korea and Singapore (the "Territory").

Under the terms of the Everest License Agreement, the Company received from Everest Medicines an upfront cash payment of $7.0 million in the first quarter of 2018 and a cash payment of $2.5 million related to Everest Medicines' submission of an Investigational New Drug Application, or IND, with the Chinese Food and Drug Administration in June 2018. In 2019, the Company expects to receive an additional cash payment of $3.0 million related to Everest Medicine's initiation of a Phase 3 clinical trial. The Company has determined that it is probable that this milestone will be achieved and that a significant revenue reversal will not occur, based on the Chinese FDA having furnished to Everest Medicines an IND approval letter to initiate a Phase 3 clinical trial in October 2018.

The Company is also eligible to receive up to an aggregate of $11.0 million in future clinical development milestone payments and up to an aggregate of $20.0 million in sales milestone payments. There can be no guarantee that any such milestones or sales thresholds will in fact be met. The Company is obligated to make certain payments to Harvard based on amounts received from Everest Medicines under the Everest License Agreement pursuant to the existing license agreement by and between Harvard and the Company.

The Company will also be entitled to receive low double-digit tiered royalties on sales in the Territory, if any, of products containing eravacycline. Royalties are payable with respect to each jurisdiction in the Territory until the latest to occur of: (i) the last-to-expire of specified patent rights in such jurisdiction in the Territory; (ii) expiration of marketing or regulatory exclusivity in such jurisdiction in the Territory; or (iii) ten (10) years after the first commercial sale of a product in such jurisdiction in the Territory. In addition, royalties payable under the Everest License Agreement will be subject to reduction on account of generic competition and after patent expiry in a jurisdiction if required by applicable law, with any such reductions capped at certain percentages of the amounts otherwise payable during the applicable royalty payment period.

Under the terms and conditions of the Everest License Agreement, Everest Medicines will be solely responsible for the development and commercialization of licensed products in the Territory. The Company agreed to manufacture clinical material, which will be paid by Everest at the Company's cost, as well as commercial supply, which will be paid by Everest at cost plus a reasonable margin.

In evaluating the recognition of revenue under the Agreement, the Company identified the following three performance obligations under the Agreement: (i) exclusive license to develop and commercialize eravacycline for the treatment of complicated intra-abdominal infections and other potential, future indications, in the Territory, (ii) provision of information and technical assistance related to the know-how transfer for the development of eravacycline; and (iii) provision of clinical supply to Everest Medicines.

The Company evaluated the Everest License Agreement under Topic 606 at the time of execution of the arrangement. Based on that evaluation, the upfront fee of $7.0 million represented the amount of the consideration to be included in the transaction price, which was allocated to the identified performance obligations. Subsequent to

execution, the Company determined that the milestones for the Chinese IND and Phase 3 clinical trial were probable to be achieved and that a significant revenue reversal would not occur, and included the payment amounts of $2.5 and $3.0 million, respectively, in the transaction price.

No other clinical milestones, regulatory milestones, sales-based milestones or sales royalties have been included in the transaction price, as these milestones were not considered probable at execution or each reporting period thereafter given Everest Medicines relatively short operating history, the uncertainty of regulatory processes in China and that commercial sales have not commenced. The Company determined that the license and related know-how were a combined performance obligation as the license is not distinct without the provision of the related know-how transfer. The Company's requirement to manufacture clinical supply for Everest Medicines is dependent on Everest Medicines' future purchases, the payment for which was determined to be at cost and therefore potentially represents a material right. However, based on the amount of clinical supply expected to be ordered by Everest Medicines, the Company estimated that the value of this right was immaterial.

The Company satisfied all performance obligations during 2018, therefore recognizing $12.7 million in license and collaboration revenue.

Patheon UK Limited Master Manufacturing Services Agreement

In June 2017, the Company and Patheon UK Limited and certain of its affiliates (“Patheon”) entered into a master manufacturing services agreement. Under the Patheon agreement, the Company is responsible for supplying the active pharmaceutical ingredient for eravacycline to Patheon, and Patheon is responsible for manufacturing eravacycline, conducting quality control, quality assurance, analytical testing and stability testing and packaging. The Company and Patheon entered into two related product agreements pursuant to the Patheon agreement that govern the terms and conditions of Patheon’s manufacture of commercial supplies of eravacycline at Patheon’s Greenville, North Carolina and Ferentino, Italy manufacturing sites. Pursuant to the Patheon agreement, the Company has agreed to order from Patheon at least a certain percentage of its annual commercial requirements for eravacycline in the United States and European Union each year for the term of the Patheon agreement. The Patheon agreement has an initial term ending December 31, 2022, and will automatically renew after the initial term for successive terms of two years each, unless either party gives notice of its intention to terminate at least 18 months prior to the end of the then current term. The Company may terminate a product agreement upon 30 days’ prior written notice under certain circumstances.

Finorga SAS Commercial Supply Agreement

In October 2017, the Company and Finorga SAS (“Novasep”) entered into a commercial supply agreement. Under the agreement, Novasep will, pursuant to accepted purchase orders entered into under the agreement, manufacture for commercial supply the active pharmaceutical ingredient for eravacycline. This agreement has an initial term ending October 16, 2022, and will automatically renew after the initial term, unless either party gives notice of its intention to terminate at least 18 months prior to the end of the then current term. The Company may terminate the Novasep agreement upon 30 days’ prior written notice under certain circumstances.

Government Grant and Contracts

BARDA Contract for Eravacycline

The Company has received funding for its lead product candidate, eravacycline, under an award to CUBRC from BARDA. In January 2012, BARDA awarded a five-year contract that provides for up to a total of $67.3 million in funding for the development, manufacturing and clinical evaluation of eravacycline for the treatment of disease caused by bacterial biothreat pathogens. The funding under the BARDA Contract is also being used for the development, manufacturing and clinical evaluation of eravacycline to treat certain infections caused by life-threatening multidrug-resistant bacteria.

In connection with the BARDA Contract, in February 2012, the Company entered into a cost-plus-fixed-fee subcontract with CUBRC which currently expires on March 30, 2019 under which the Company may receive funding of up to approximately $41.8 million, reflecting the portion of the BARDA Contract funding that may be paid to the Company for its activities.

Although the BARDA Contract and the Company’s subcontract with CUBRC under the BARDA Contract have terms which currently expire on March 30, 2019, BARDA is entitled to terminate the project for convenience at any time, and is not obligated to provide continued funding beyond current-year amounts from Congressionally approved annual appropriations. To the extent that BARDA ceases to provide funding of the program to CUBRC, CUBRC has the right to cease providing funding to the Company. Committed funding from CUBRC under the Company’s BARDA subcontract is up to $41.8 million through March 30, 2019, the current contract end date, as a result of the exercise of

several options by BARDA under the BARDA Contract. Total funds of $39.6 million had been received by the Company through December 31, 2018 under this contract. During the years ended December 31, 2018 and 2017, the Company recognized revenue of $1.5 million and $5.5 million, respectively, from the Company's subcontract under the BARDA Contract.

NIAID Grant and Contract for TP-271

The Company has received funding for its preclinical compound TP-271 under two awards to CUBRC from NIAID for the development, manufacturing, and clinical evaluation of TP-271 for respiratory diseases caused by biothreat and antibiotic-resistant public health pathogens, as well as bacterial pathogens associated with community-acquired bacterial pneumonia:

- the NIAID Grant awarded in July 2011 that provided up to a total of approximately $2.9 million over five years; and
- the NIAID Contract awarded in September 2011 that provides up to a total of approximately $35.8 million in funding over five years.

In connection with the NIAID Grant, in November 2011, CUBRC awarded the Company a no-fee subaward of approximately $0.9 million, reflecting the portion of the NIAID Grant funding that may be paid to the Company for its activities. Through December 31, 2018, the Company had received all committed funding of $0.9 million from CUBRC under the Company's subaward with respect to the NIAID Grant.

In connection with the NIAID Contract, in October 2011, the Company entered into a cost-plus-fixed-fee subcontract with CUBRC which currently expires on March 31, 2019 under which the Company may receive funding of up to approximately $16.9 million, reflecting the portion of the NIAID Contract funding that may be paid to the Company for its activities.

Although the NIAID Contract and the Company's subcontract with CUBRC under the NIAID Contract have terms which currently expire on March 31, 2019. NIAID is entitled to terminate the project for convenience at any time, and is not obligated to provide continued funding beyond the respective expiration dates. To the extent that NIAID ceases to provide funding of the programs to CUBRC, CUBRC has the right to cease providing funding to the Company. As of December 31, 2018, committed funding from CUBRC under the Company's subcontract with respect to the NIAID Contract is $16.6 million, of which $15.7 million had been received through December 31, 2018.

During the years ended December 31, 2018 and 2017, the Company recognized revenue of $2.5 million and $3.5 million, respectively, from the Company's subcontract under the NIAID Contract. During the year ended December 31, 2017 the Company recognized $9,000 from the Company's subaward under the NIAID Grant.

CARB-X Award for TP-6076

In March 2017, CARB-X selected the Company to receive up to $4.0 million in research funding over eighteen months for TP-6076. In connection with this funding, the Company entered into a cost reimbursement Sub-Award Agreement (the "Sub-Award Agreement") with the Trustees of Boston University, the administrator of the program. The Company began recognizing revenue from the Sub-Award Agreement in April 2017. During the years ended December 31, 2018 and 2017, the Company recognized revenue of $2.0 million and $0.7 million, respectively, under this Sub-Award Agreement. Although this Sub-Award Agreement expired by its terms on December 31, 2018, we expect to reach an agreement with CARB-X to extend the performance date out to June 30, 2019 (pending an amendment that would take the performance date out to June 30, 2019, the project can be terminated for convenience at any time, subject to 30 days prior written notice.

(4) Property and Equipment

Property and equipment at December 31, 2018 and 2017 consisted of the following (in thousands):

	Estimated Useful Life	December 31,	
	In Years	2018	2017
Laboratory equipment	5	$3,278	$3,101
Furniture and fixtures	5	509	509
Office and computer equipment	3	217	208
Leasehold improvements		923	923
Property and equipment, gross		4,927	4,741

Less accumulated depreciation and amortization	(3,806)	(3,346)
Property and equipment, net	$1,121	$1,395

Depreciation and amortization expense related to property and equipment for the years ended December 31, 2018, 2017 was $479,000 and $431,000 , respectively.

(5) Accrued Expenses

Accrued expenses at December 31, 2018 and 2017 consisted of the following (in thousands):

	December 31, 2018	December 31, 2017
Drug supply and development	$ 3,901	$ 2,298
Salaries and benefits	3,801	4,137
Professional fees	1,178	1,911
Commercial	910	—
License payments	617	—
Clinical trial related	146	3,401
Other	1,194	812
Total	$ 11,747	$ 12,559

(6) Stockholders' Equity

In January 2017, the Company entered into a Controlled Equity Offering Sales Agreement (the "Sales Agreement"), with Cantor Fitzgerald & Co. as sales agent ("Cantor"). In July 2017, the Company entered into an amendment to the Sales Agreement to increase the maximum aggregate offering price of the shares of common stock that it may issue and sell from time to time under the Sales Agreement from $40,000,000 to $80,000,000.

Under the Sales Agreement, as amended (the "Amended Sales Agreement"), Cantor may sell shares of the Company's common stock by methods deemed to be an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, including sales made directly on The Nasdaq Global Select Market or on any other existing trading market for the Company's common stock.

The Company is not obligated to make any sales of shares of its common stock under the Amended Sales Agreement. The Company or Cantor may suspend or terminate the offering of shares of the Company's common stock upon notice to the other party and subject to other conditions. The Company pays Cantor a commission rate equal to 3.0% of the gross proceeds per share sold.

As of December 31, 2018, the Company had sold an aggregate of 6,110,446 shares of common stock under the Sales Agreement, at an average selling price of approximately $6.49 per share for aggregate gross proceeds of $39.6 million and net proceeds of $38.2 million after deducting the sales commissions and offering expenses. As of March 13, 2019, $40.4 million of common stock remained available to be sold under the Amended Sales Agreement, subject to certain conditions specified therein.

On August 2, 2017, the Company sold 10,000,000 shares of common stock in an underwritten public offering at an offering price to the public of $6.50 per share, resulting in net proceeds to the Company of $60.7 million after deducting underwriting discounts and commissions of $3.9 million and offering costs of $0.4 million. In connection with the offering, the Company granted the underwriters an option to purchase up to an additional 1,500,000 shares on the same terms and conditions as the offering, pursuant to which the underwriters exercised an option to purchase 107,000 additional shares on August 25, 2017, resulting in additional net proceeds to the Company of approximately

$0.7 million after deducting underwriting discounts and commissions.

(7) Stock-based Compensation

In February 2013, the Company's board of directors and stockholders approved, effective upon the closing of the IPO, the 2013 Stock Incentive Plan (the "2013 Plan"). Under the 2013 Plan, the Company may grant incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock, restricted stock units and other stock-based awards for the purchase of that number of shares of Common Stock equal to the sum of (i) 1,688,777 shares of Common Stock, (ii) 258,265 shares of Common Stock that were reserved for issuance under the 2006 Plan that remained available for issuance under the 2006 Plan upon the closing of the IPO, (iii) any shares of Common Stock subject to awards under the 2006 Plan which awards expire, terminate or are otherwise surrendered, canceled, forfeited or repurchased by the Company without having been fully exercised or resulting in any Common Stock being issued. In addition, the number of shares of Common Stock that may be issued under the 2013 Plan is subject to automatic annual increases, to be added on January 1 of each year from January 1, 2014 through and including January 1, 2023, equal to the number of shares that is the lesser of (a) 3,000,000, (b) 4% of the then outstanding shares of Common Stock or (c) an amount determined by the Company's board of directors.. In January 2019, the number of shares authorized for issuance under the 2013 Plan increased by 2,147,192 shares.

Terms of stock award agreements, including vesting requirements, are determined by the board of directors, subject to the provisions of the 2013 Plan. Options granted by the Company typically vest over a four year period. Certain of the options are subject to acceleration of vesting in the event of certain change of control transactions. The options are exercisable from the date of grant for a period of ten years. For options granted prior to the Company's IPO, the exercise price equaled the estimated fair value of the Common Stock as determined by the board of directors on the date of grant. For options granted subsequent to the Company's IPO, the exercise price equaled the closing price of the Company's stock on the Nasdaq Global Select Market on the date of grant.

Stock option activity at December 31, 2018 and changes during the year then ended are presented in the table and narrative below (in thousands, except share and per share data):

	Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value
Options outstanding at December 31, 2017	5,997,794	$ 13.33	7.14	$ 6,065
Granted	2,575,725	5.48		
Exercised	(115,064)	2.35		
Canceled	(1,136,019)	10.67		
Options outstanding at December 31, 2018	7,322,436	$ 11.16	7.45	$ 5
Options exercisable at December 31, 2018	3,865,419	$ 15.49	6.45	$ 5

The aggregate intrinsic value in the table above represents the difference between the Company's closing common stock price on the last trading day during the year ended December 31, 2018 and the exercise price of the options, multiplied by the number of in-the-money options. The total intrinsic value of options exercised in the years ended December 31, 2018 and 2017 was $0.4 million and $0.2 million, respectively. As of December 31, 2018, there was $13.4 million of total unrecognized stock-based compensation cost related to employee unvested stock options granted under the 2006 Plan and the 2013 Plan. The Company expects to recognize that cost over a remaining weighted-average period of 2.4 years.

Since the Company completed its IPO on March 25, 2013, it has not had sufficient historical data to support a calculation of volatility and expected life. As such, the Company has used a weighted-average volatility considering the Company's own volatility and the volatilities of a representative group of publicly traded companies. For purposes of identifying similar entities, the Company selected a group of publicly traded life science/biotechnology companies based on their disease focus, stage of development, number of compounds in clinical trials and number of years as a publicly-traded company. The risk-free interest rate is based on the U.S. Treasury yield curve in effect at the time of grant, commensurate with the expected life assumption. The expected life of stock options granted represents the weighted-average period of time that stock options granted are expected to be outstanding determined using the simplified method for employee grants. For non-employee grants, the expected life is equal to the remaining contractual term. The expected life is applied to the stock option grant group as a whole, as the Company does not expect substantially different exercise or post-vesting termination behavior among its employee population.

The Company estimates the fair value of each employee and director stock option award on the grant date using the Black-Scholes option-pricing model based on the following assumptions:

	Years Ended December 31,	
	2018	2017
Volatility factor	91.45%-97.39%	89.24%-90.56%
Expected life (in years)	5.31-6.11	5.31-6.11
Risk-free interest rate	2.41%-3.04%	1.78%-2.18%
Dividend yield	0%	0%

Compensation cost for stock options and restricted stock units granted to employees is based on the estimated grant-date fair value and is recognized over the vesting period of the applicable option on a straight-line basis. Stock-based compensation expense related to stock options and restricted stock units granted to employees was $13.0 million and $12.0 million during the years ended December 31, 2018 and 2017, respectively.

Using the Black-Scholes option-pricing model, the weighted-average grant date fair values of options granted to employees for the years ended December 31, 2018 and 2017 was $4.18 and $3.37, respectively.

Stock-based compensation expense recognized in the Company's consolidated statements of operations during the periods presented was as follows (in thousands):

	Year Ended December 31,	
	2018	2017
Research and development	$5,721	$5,768
General and administrative	7,408	6,195
Total	$13,129	$11,963

	Year Ended December 31,	
	2018	2017
Stock options	$10,925	$11,156
Restricted stock units	2,089	686
Employee stock purchase plan	115	121
Total	$13,129	$11,963

Restricted Stock Units

In April 2018, the Company granted restricted stock units to employees. These restricted stock units vest in quarterly increments over one to two years, subject to continued employment with the Company and had a grant date fair value of $3.04 per share, which was the closing price of the Company's common stock on the date of grant.

In January 2018 and 2017, the Company issued to certain employees 284,000 and 175,000 restricted stock units, respectively, which vest based on service and performance conditions. None of these awards fully vested during years ended December 31, 2018 and 2017. Vesting of these awards is contingent on the occurrence of certain milestone events and fulfillment of any remaining service condition. As a result, the related compensation cost is recognized as an expense when achievement of the milestone is considered probable over the remaining requisite service period. During 2018, certain of the performance conditions were achieved or deemed probable of achievement, resulting in recognition of related compensation cost of $0.3 million.

The following table summarizes the restricted stock activity for the year ended December 31, 2018:

	Shares	Weighted Average Grant Date

		Fair Value
Unvested at December 31, 2017	282,034	$ 6.09
Granted	937,460	4.02
Cancelled	(70,526)	5.07
Vested/Released	(68,528)	8.47
Unvested at December 31, 2018	1,080,440	4.21

As of December 31, 2018, there was $1.1 million of total unrecognized stock-based compensation expense related to restricted stock units granted under the Plan. The expense is expected to be recognized over a weighted-average period of 1.0 year.

(8) Employee Stock Purchase Plan

The ESPP was approved by the Company's stockholders on June 12, 2014 and allows the Company to sell an aggregate of 300,000 shares of common stock. The ESPP allows eligible employees to purchase common stock at a price per share equal to 85% of the lower of the fair market value of the common stock at the beginning or end of each period during the term of the ESPP. The offering periods are six months each from May to November and from November to May of each calendar year. Pursuant to the ESPP, the Company sold a total of 86,145 shares of common stock during the year ended December 31, 2018 under the ESPP at purchase prices of $3.15, and $1.62, respectively, which represented 85% of the closing price of the Company's common stock on May 14, 2018, and November 14, 2018, respectively. Pursuant to the ESPP, the Company sold a total of 77,604 shares of common stock during the year ended December 31, 2017 under the ESPP at purchase prices of $3.43, and $5.10, respectively, which represented 85% of the closing price of the Company's common stock on May 12, 2017, and November 14, 2017, respectively. The Company records stock-based compensation expense under the ESPP based on the fair value of the purchase rights using the Black-Scholes option pricing model. The total stock-based compensation expense recorded as a result of the ESPP was $115,000 and $121,000 during the years ended December 31, 2018 and 2017, respectively.

(9) Debt Facility

On November 2, 2018, the Company entered into a loan and security agreement (the "Loan Agreement") with Solar Capital Ltd., as collateral agent and lender, and the other lenders named therein (Solar Capital Ltd. and the other lenders collectively, the "Lenders"). The Lenders have agreed to make available to the Company term loans in an aggregate principal amount of up to $75.0 million under the Loan Agreement. The Company plans to use the proceeds of the term loans to support commercial launch of Xerava as well as for working capital and general corporate purposes. The Loan Agreement provides a term loan commitment of $50.0 million in two potential tranches: (i) a $30.0 million Term A loan facility funded on November 2, 2018 and (ii) a $20.0 million Term B loan facility to be funded at the request of the Company no later than October 31, 2020, subject to (A) the Company having unrestricted net cash proceeds of not less than $50 million from the issuance and sale of common stock and/or from other business activities and (B) the Company having product revenue greater than or equal to $14.0 million on a six month trailing basis prior to September 30, 2020. Both of these term loans have a maturity date of May 2, 2023. The Loan Agreement also provides access to an additional Term C loan facility in the amount of $25.0 million, to be funded at the Lenders' sole discretion.

Borrowings under all three loan facilities bear interest at a floating per annum rate equal to the 1 Month LIBOR Rate plus 7.25%. The Company is permitted to make interest-only payments on the initial $30.0 million Term A loan for the fifteen (15) months following the funding date. The interest-only period can be extended by an additional nine (9) months subject to certain conditions being met, including a 12-month trailing revenue milestone of $8.5 million by December 31, 2019; and by an additional six (6) months if the Company has met certain other conditions, including a 6-month trailing revenue milestone of $14.0 million by September 30, 2020 and raising $50.0 million in new capital. The term of the combined facility will be 54 months, with repayment paid in equal monthly installments commencing at the end of the resulting interest-only period as outlined above through the end of the 54-month term.

The Company is obligated to pay a final fee equal to 4.00% of the aggregate amount of the term loans funded, to occur upon the earliest of (i) the maturity date, (ii) the acceleration of the term loans, and (iii) the prepayment of the term loans. The Company has the option to prepay all, but not less than all of the outstanding principal balance of the term loans under the Loan Agreement. If the Company prepays all or a portion of the term loans prior to the maturity date, it will pay the Lenders a prepayment penalty fee based on a percentage of the outstanding principal balance, equal to 3% if the payment occurs on or before 12 months after the initial funding date, 2% if the prepayment occurs more than 12 months after, but on or before 24 months after, the initial funding date, or 1% if the prepayment occurs

more than 24 months after the initial funding date.

In connection with the Loan Agreement and the funding of the Term A loan facility, the Company issued to the Lenders warrants to purchase an aggregate of 414,365 shares of the Company's common stock, equal to 3.00% of the term loan funded divided by the exercise price of $2.172. The Company is obligated to issue additional warrants to the Lenders in the event the Term B loan facility and/or the Term C loan facility is funded. Those warrants shall also be equal to 3.00% of the term loan funded. The warrants are exercisable at the option of the holder and the exercise price will be the lesser of (a) the 10-day trailing average of the Company's common stock price, as determined as of the close of business day immediately prior to the funding date of the respective term loan, and (b) the Company's common stock price, as determined as of the close of business day immediately prior to the funding date of the respective term loan. Each warrant will terminate 10 years from the date of its original issuance. The warrants were equity classified with a fair value of $0.8 million at issuance and recorded to additional paid in capital.

The Company's obligations under the Loan Agreement are secured by a first priority security interest in substantially all of its assets. The Loan Agreement contains customary representations, warranties and covenants and also includes customary events of default, including payment defaults, breaches of covenants, change of control and a material adverse change default. The Company has agreed to maintain cash on hand at all times equal to $10.0 million plus an amount equal to 90 days aged accounts payable subject to certain exceptions, or it is in breach of the Loan Agreement.

Upon the occurrence of an event of default, a default interest rate of an additional 4.00% per annum may be applied to the outstanding loan balances, and the Lenders may declare all outstanding obligations immediately due and payable and exercise all of its rights and remedies as set forth in the Loan Agreement and under applicable law.

The Company recorded interest expense related to the loan facility of $624,000 for the year ended December 31, 2018. The fair value of the loan at December 31, 2018 approximates its face amount given the close proximity of execution to December 31, 2018.

The Company evaluated the accounting for the Loan Agreement and identified an embedded derivative related to repayment upon default, which it evaluated and deemed immaterial. The Company will reassess this conclusion at each reporting period.

Future principal debt payments on the loan payable are as follows (in thousands):

	December 31, 2018
2019	$ —
2020	8,462
2021	9,231
2022	9,231
2023	3,076
Total principal payments	30,000
Final fee due at maturity in 2023	1,200
Total principal and final fee payments	31,200
Unamortized debt issuance costs and final fee	(2,909)
Loan payable, long term	$ 28,291

(10) Income Taxes

The Company accounts for income taxes under ASC 740, Accounting for Income Taxes. Deferred income tax assets and liabilities are determined based upon differences between financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse.

Loss before income tax (benefit) provision consists of the following (in thousands):

	Year ended December 31,	
	2018	2017

United States	$(61,046)	$(94,748)
Foreign	(11,112)	(20,004)
Total loss before income taxes	$(72,158)	$(114,752)

For the years ended December 31, 2018 and 2017 the Company did not have a current or deferred income tax expense or benefit.

A reconciliation of the Federal statutory tax rate of 21% to the Company’s effective income tax rate follows:

	Year ended December 31,	
	2018	2017
Statutory tax rate	(21.00)%	(34.00)%
State taxes, net of federal benefits	(4.10)%	(4.37)%
Permanent differences	2.30 %	1.18 %
Credits	(1.80)%	(0.96)%
Intellectual property transfer	(3.80)%	—
Change in valuation allowance	25.20 %	(11.04)%
Foreign rate differential	3.20 %	5.93 %
Federal Rate Change - Tax Reform	—	43.26 %
Effective tax rate	— %	— %

On December 22, 2017, the Tax Cuts and Jobs Act ("the Act") was enacted in the United States. The Act reduces the U.S. federal corporate tax rate from 34% to 21%, requires companies to pay a one-time transition tax on earnings of certain foreign subsidiaries that were previously tax deferred and creates new taxes on certain foreign sourced earnings. For the year ended December 31, 2018, we recognized no transition tax and have not recorded any additional taxes on the outside basis difference of our foreign subsidiary as our investment in the foreign subsidiary is essentially permanent in duration. Determining the amount of unrecognized deferred tax liability is not practicable.

In connection with the Act, the Company remeasured certain deferred tax assets and liabilities based on the rates at which they are expected to reverse in the future, which is generally 21%. The remeasurement of the Company's deferred tax balance was primarily offset by application of its valuation allowance. As of December 31, 2018, the Company had completed its accounting for all of the tax effects of the enactment of the Act; including the effects on its existing deferred tax balances. The Company had not recognized any material adjustment to the provisional estimate that was previously recorded related to the Act.

As of December 31, 2018, the Company had federal net operating loss carryforwards of approximately $428.0 million and state net operating loss carryforwards of $395.6 million, which are available to reduce future taxable income. Federal net operating loss carryforwards of $383.2 million will expire are various dates through 2037. $44.9 million of the federal net operating loss carryforward can be carried forward indefinitely. The state net operating loss carryforward of $395.6 million will expire at various dates through 2038.

The Company also had federal tax credits of $8.4 million and state tax credits of $2.9 million, which may be used to offset future tax liabilities. The net operating loss (NOL) and tax credit carryforwards will expire at various dates through 2038.

The NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. In addition, the Company has not, as yet, conducted a study of research and development (“R&D”) credit

carryforwards. This study may result in an adjustment to the Company's R&D credit carryforwards. Any adjustment as a result of such study would be fully offset by a decrease in the Company's valuation allowance.

The principal components of the Company's deferred tax assets are as follows (in thousands):

	Year ended December 31,	
	2018	2017
Deferred tax assets:		
Net operating loss carryforwards	$114,097	$102,942
Equity-based compensation	8,836	7,073
Accrued expenses	149	142
Depreciation	116	52
Start up costs	5	8
Intangibles	4,578	967
Research and development credits and carryforwards	10,649	9,079
Deferred tax assets	138,430	120,263
Less valuation allowance	(138,430)	(120,263)
Net deferred tax assets	$—	$—

ASC 740 requires a valuation allowance to reduce the deferred tax assets reported, if based on the weight of available evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a valuation allowance against its deferred tax assets at December 31, 2018 and 2017, respectively, because the Company's management has determined that is it more likely than not that these assets will not be realized. The $18.2 million increase in the valuation allowance in 2018 primarily relates to the loss incurred by the Company in this period.

ASC 740 clarifies the accounting for uncertainty in income taxes recognized in an enterprise's financial statement by prescribing the minimum recognition threshold and measurement of a tax position taken or expected to be taken in a tax return. The Company had gross tax-effected unrecognized tax benefits of $1.3 million and $1.1 million at December 31, 2018 and 2017, respectively. Unrecognized tax benefits represent tax positions for which reserves have been established. A full valuation allowance has been provided against the Company's deferred tax assets, so that the effect of any unrecognized tax benefits would simply be to reduce the gross amount of the deferred tax asset and the corresponding valuation allowance. The Company anticipates that the amount of unrecognized tax benefits recorded will not change in the next twelve months.

As of December 31, 2018 and 2017, the Company had no accrued interest or penalties related to uncertain tax positions.

The aggregate changes in gross unrecognized tax benefits during the years ended December 31, 2018 and 2017 were as follows (in thousands):

	Year ended December 31,	
	2018	2017

Balance at beginning of year	$1,107	$967
Increases for tax positions taken during current period	130	152
Increases for tax positions taken in prior periods	54	—
Decreases for tax positions taken during current period	—	(12)
Decreases for tax positions taken in prior periods	—	—
Balance at end of year	$1,291	$1,107

The Company is currently open to examination under the statute of limitations by the Internal Revenue Service and state jurisdictions for the tax years ended 2015 through 2017. Carryforward tax attributes generated in years past may still be adjusted upon future examination if they have or will be used in a future period. The Company is currently not under examination by the Internal Revenue Service or any other jurisdictions for any tax years.

(11) Commitments and Contingencies

Lease Commitments

On March 24, 2015, the Company amended its existing operating lease to expand its existing premises by an additional 13,711 square feet of office and laboratory space for a total of 29,610 square feet. The effective date of this amendment was April 1, 2015. On March 31, 2015, the Company canceled an existing sublease entered into in September 2014 covering 15,174 square feet of office and laboratory space.

On June 18, 2015, the Company further amended its existing operating lease to expand its leased premises by an additional 7,828 square feet of office and laboratory space for a total of 37,438 square feet. The lease for the additional office and laboratory space was effective as of August 1, 2015. In connection with the amendment, the lease term was extended from November 30, 2016 to November 30, 2019.

In the third quarter of 2016, the Company entered into a sublease with respect to a portion of its principal facilities with an unrelated third party. The term of the sublease expires in November 2019, with the sublessee obligated to pay rent to the Company that approximates the rent the Company is currently paying to its landlord with respect to such portion of its facility.

On November 29, 2018, the Company amended its existing operating lease to extend the lease term through November 30, 2022.

As of December 31, 2018, the aggregate minimum future rent payments under the lease agreement, net of the sublease agreement, are as follows (in thousands):

	December 31, 2018
2019	1,806
2020	1,875
2021	1,913
2022	1,785
Total minimum lease payments	$ 7,379

The Company recorded $1.4 million and $1.4 million in rent expense for the years ended December 31, 2018 and 2017, respectively

(12) Employee Benefit Plan

In 2007, the Company established the Tetraphase Pharmaceuticals, Inc. 401(k) Plan (the “401(k) Plan”) for its employees, which is designed to be qualified under Section 401(k) of the Internal Revenue Code. Eligible employees are permitted to contribute to the 401(k) Plan within statutory and 401(k) Plan limits. During 2014, the Company began to make matching contributions of 50% of the first 6% of employee contributions. The Company made matching contributions of $402,000 and $354,000 for the years ended December 31, 2018 and 2017, respectively.

(13) Legal Proceedings

In January 2016 and March 2016, two securities class action lawsuits were filed against the Company, the Company's chief executive officer, the Company's former chief operating officer and the Company's former chief financial officer, in the United States District Court for the District of Massachusetts. In May 2016, the court consolidated the two lawsuits and appointed lead plaintiffs and lead counsel. The lead plaintiffs filed a consolidated amended complaint in July 2016 and filed a second consolidated amended complaint in August 2016. The second amended complaint was brought on behalf of an alleged class of those who purchased the Company's common stock between March 5, 2015 and September 8, 2015, and alleged claims arising under Sections 10 and 20 of the Exchange Act of 2934, as amended. The complaint generally alleged that the defendants violated the federal securities laws by, among other things, making material misstatements or omissions concerning IGNITE2. The complaint sought, among other relief, unspecified compensatory damages, attorneys' fees and costs. In October 2016, the Company filed a motion to dismiss the second amended complaint in its entirety, which plaintiffs opposed. The Company's motion to dismiss was granted by the United States District Court for the District of Massachusetts in May 2017. In July 2017 plaintiffs appealed this decision to the United States Court of Appeals for the First Circuit, or the First Circuit. In November 2017 plaintiffs withdrew their appeal to the First Circuit.

In July 2018, a purported securities class action lawsuit was filed against us, our chief executive officer, our chief scientific officer and the underwriters of our July 2017 public offering, in the United States District Court for the Southern District of New York. The complaint is brought on behalf of an alleged class of those who purchased our securities pursuant and/or traceable to our

July and August 2017 public offering and those who purchased our securities between March 8, 2017 and February 13, 2018. The complaint purports to allege claims arising under Sections 10 and 20 of the Exchange Act of 1934, as amended, and Sections 11 and 15 of the Securities Act of 1933, as amended. The complaint generally alleges that the defendants violated the federal securities laws by, among other things, making material misstatements or omissions concerning IGNITE3. The complaint seeks, among other relief, unspecified compensatory damages, attorneys' fees, and costs. The defendants have moved to transfer the lawsuit to the United States District Court for the District of Massachusetts. We believe we have valid defenses against these claims, and will engage in a vigorous defense of such litigation and therefore a loss is not probable as of December 31, 2018.

(14) Quarterly Results (Unaudited)

	Three Months Ended March 31, 2018	June 30, 2018	September 30, 2018	December 31, 2018
	(in thousands, except per share data) (unaudited)			
Revenues:				
Product revenues, net	$—	$—	$ —	$ 178
License and collaboration revenues	—	9,500	—	3,177
Government revenues	1,891	2,079	1,151	928
Total revenues	1,891	11,579	1,151	4,283
Expenses:				
Cost of revenue - product	—	—	—	130
Cost of revenue - intangible asset amortization	—	—	—	98
Research and development expenses	18,127	14,370	11,665	10,717
Selling, general and administrative expenses	5,705	7,165	9,481	14,727
Total expenses	23,832	21,535	21,146	25,672
Loss from operations	(21,941)	(9,956)	(19,995)	(21,389)
Interest income	365	413	437	532
Interest expense	—	—	—	(624)
Net loss	(21,576)	(9,543)	(19,558)	(21,481)
Net loss per share—basic and diluted	$(0.42)	$(0.18)	$ (0.37)	$ (0.40)

	Three Months Ended March 31, 2017	June 30, 2017	September 30, 2017	December 31, 2017
	(in thousands, except per share data)			

	(unaudited)			
Revenue	$1,485	$1,586	$ 4,067	$ 2,528
Expenses:				
Research and development	25,947	28,513	28,777	18,469
General and administrative	5,133	5,065	5,600	7,877
Total expenses	31,080	33,578	34,377	26,346
Loss from operations	(29,595)	(31,992)	(30,310)	(23,818)
Interest income	137	181	302	343
Net loss	(29,458)	(31,811)	(30,008)	(23,475)
Net loss per share—basic and diluted	$(0.79)	$(0.83)	$ (0.63)	$ (0.46)

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, with the participation of our Chief Executive Officer and Senior Vice President, Finance, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2018. In designing and evaluating our disclosure controls and procedures, management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applied its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Chief Executive Officer and Senior Vice President, Finance concluded that as of December 31, 2018, our disclosure controls and procedures were (1) designed to ensure that material information relating to us is made known to our management including our principal executive officer and principal financial officer by others, particularly during the period in which this Annual Report on Form 10-K was prepared and (2) effective, in that they provide reasonable assurance that information required to be disclosed by us in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms.

The certifications of our principal executive officer and principal financial officer attached as Exhibits 31.1 and 31.2 to this report include, in paragraph 4 of such certifications, information concerning our disclosure controls and procedures and internal controls over financial reporting.

Internal Control Over Financial Reporting

(a) 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 Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel, 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 the assets of the company;
- 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
- 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. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. 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.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of

the Treadway Commission in Internal Control—Integrated Framework (2013 framework) (COSO). Based on its assessment, management believes that, as of December 31, 2018, our internal control over financial reporting is effective at the reasonable assurance level.

Ernst and Young LLP, our independent registered public accounting firm has audited the consolidated financial statements included in this Annual Report on Form 10-K and, as part of the audit, has issued a report on the effectiveness of our internal control over financial reporting as of December 31, 2018, which report is included herein.

(b) Report of Independent Registered Public Accounting Firm on Internal Control over Financial Reporting

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Tetraphase Pharmaceuticals, Inc.

Opinion on Internal Control over Financial Reporting

We have audited Tetraphase Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2018, 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, Tetraphase Pharmaceuticals, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2018, 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, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2018, and the related notes and our report dated March 15, 2019 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

Boston, Massachusetts

March 15, 2019

(c) Changes in Internal Control Over Financial Accounting

There were no changes in our internal control over financial reporting that occurred during the quarter ended December 31, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. Other Information

None.

PART III

ITEM 10. Directors, Executive Officers and Corporate Governance

The information required by this Item 10 will be contained in the sections entitled “Election of Directors” and “Section 16(a) Beneficial Ownership Reporting Compliance” appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein. The information required by this item concerning our code of ethics is set forth in the section entitled “Code of Business Conduct and Ethics” appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein. The information required by this item relating to executive officers is set forth in the section entitled “Executive Officers” appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

ITEM 11. Executive Compensation

The information required by this Item 11 will be contained in the sections entitled “Executive and Director Compensation” and “Compensation Committee Interlocks and Insider Participation” appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

ITEM 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item 12 will be contained in the sections entitled “Ownership of Our Common Stock” and “Executive and Director Compensation—Equity Compensation Plan Information” appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

ITEM 13. Certain Relationships and Related Person Transactions, and Director Independence

The information required by this Item 13 will be contained in the sections entitled “Certain Relationships and Related Person Transactions” appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

ITEM 14. Principal Accounting Fees and Services

The information required by this Item 14 will be contained in the section entitled “Corporate Governance—Principal Accountant Fees and Services” appearing in the definitive proxy statement we will file in connection with our 2019 Annual Meeting of Stockholders and is incorporated by reference herein.

PART IV

ITEM 15. Exhibits and Financial Statement Schedules

(a) Documents filed as part of Form 10-K.

(1) Financial Statements

Report of Independent Registered Public Accounting Firm

Consolidated Balance Sheets

Consolidated Statements of Operations and Comprehensive Loss

Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)

Consolidated Statements of Cash Flows

Notes to Consolidated Financial Statements

(2) Schedules

Schedules have been omitted as all required information has been disclosed in the financial statements and related footnotes.

(3) Exhibits

The Exhibits listed in the Exhibit Index are filed as a part of this Form 10-K.

ITEM 16. Form 10-K Summary

None.

EXHIBIT INDEX

Exhibit Number	Description	Incorporated by Reference from Registrant's Form	File No.	Date Filed with the SEC	Exhibit Number
3.1	Restated Certificate of Incorporation of the Registrant	10-Q	001-35837	5/13/13	3.1
3.2	Amended and Restated Bylaws of the Registrant	10-Q	001-35837	5/13/13	3.2
4.1	Specimen certificate evidencing shares of common stock	S-1/A	333-186574	3/5/13	4.1
4.2	Form of Warrant to Purchase Stock entered into in connection with the Loan and Security Agreement, dated as of November 2, 2018	8-K	001-35837	11/5/2018	4.1
10.1#	2006 Stock Incentive Plan, as amended	S-1	333-186574	2/11/13	10.5
10.2#	Form of Incentive Stock Option Agreement under 2006 Stock Incentive Plan	S-1	333-186574	2/11/13	10.6
10.3#	Form of Nonstatutory Stock Option Agreement under 2006 Stock Incentive Plan	S-1	333-186574	2/11/13	10.7
10.4#	2013 Stock Incentive Plan	S-1/A	333-186574	3/5/13	10.8
10.5#	Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan	S-1/A	333-186574	3/5/13	10.9
10.6#	Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan	S-1/A	333-186574	3/5/13	10.10
10.7#	Form of Restricted Stock Agreement under 2013 Incentive Plan	10-K	001-35837	3/13/17	10.7
10.8#	2014 Employee Stock Purchase Plan	10-Q	001-35837	8/12/14	10.1
10.9#	Form of Nonstatutory Option Agreement for Inducement Grants	10-Q	001-35837	5/7/2015	10.3
10.10#	Offer letter, dated as of December 4, 2007, by and between the Registrant and Guy Macdonald, as amended	S-1	333-186574	2/11/13	10.11
10.11#		10-Q	001-35837	5/12/14	10.2

	Second Amendment to Offer Letter, dated as of March 5, 2014, by and between the Registrant and Guy Macdonald				
10.12#	Offer letter, dated as of June 11, 2015, by and between the Registrant and Jacques Dumas, as amended	10-K	001-35837	3/13/17	10.12
10.13#	Offer letter, dated as of December 27, 2017, by and between the Registrant and Larry Tsai	10-K	001-35837	3/6/18	10.13
10.14#	Offer Letter, dated September 21, 2017, by and between the Registrant and Kamalam Unninayar	10-Q	001-35837	11/1/17	10.2
10.15#	Offer letter, dated as of February 16, 2015, by and between the Registrant and Maria Stahl	10-Q	001-35837	5/7/15	10.2
10.16#	Form of Indemnification Agreement entered into between the Registrant and each of its directors and executive officers	S-1/A	333-186574	3/5/13	10.27
10.17	Lease Agreement, dated as of November 16, 2006, by and between the Registrant and ARE-480 Arsenal Street, LLC, as amended on September 9, 2011, March 15, 2012, September 18, 2012, November 20, 2013, March 24, 2015 and June 18, 2015	10-Q	001-35837	8/6/15	10.1

Exhibit Number	Description	Incorporated by Reference from Registrant's Form	File No.	Date Filed with the SEC	Exhibit Number
10.18	Amendment, dated September 4, 2014, to Lease Agreement, dated as of November 16, 2006, by and between the Registrant and ARE-480 Arsenal Street, LLC, as amended	10-Q	001-35837	11/10/14	10.1
10.19	Amendment, dated March 24, 2015, to Lease Agreement, dated as of November 16, 2006, by and between the Registrant and ARE-480 Arsenal Street, LLC, as amended	10-Q	001-35837	5/7/2015	10.1
10.20	Amendment, dated June 18, 2015, to Lease Agreement, dated as of November 16, 2006, by and between the Registrant and ARE-480 Arsenal Street, LLC, as amended	10-Q	001-35837	8/6/2015	10.1
10.21*	Amendment, dated November 29, 2018, to Lease Agreement, dated as of November 16, 2006, by and between the Registrant and ARE-480 Arsenal Street, LLC, as amended				
10.22†	License Agreement, dated as of August 3, 2006, by and between the Registrant and the President and Fellows of Harvard College, as amended	S-1	333-186574	2/11/13	10.20
10.23†	Amendment, dated as of December 5, 2017, by and between the Registrant and the President and Fellows of Harvard College, as amended	10-K	001-35837	3/6/18	10.22
10.24†	Subcontract Agreement, dated as of February 1, 2012, by and between the Registrant and CUBRC, Inc.	S-1	333-186574	2/11/13	10.21
10.25†	Subcontract Agreement, dated as of September 30, 2011, by and between the Registrant and CUBRC, Inc.	S-1	333-186574	2/11/13	10.22
10.26#	Offer letter, dated as of June 20, 2015, by and between the Registrant and Christopher Watt	10-K	001-35837	2/25/16	10.17
10.27†	Master Manufacturing Services Agreement, dated June 14, 2017, by and between the Registrant and Patheon UK Limited	10-Q	001-35837	8/2/17	10.1
10.28†	Commercial Supply Agreement, dated October 16, 2017, by and between the Registrant and Finorga SAS	10-Q	001-35837	11/1/17	10.1
10.29†	License Agreement, dated February 20, 2018, by and between the Registrant and Everest Medicines Limited	10-K	001-35837	3/6/18	10.28

10.30#	Offer letter, dated as of March 1, 2018, by and between the Registrant and Larry Edwards	10-K	001-35837	3/6/18	10.31
10.31	Loan and Security Agreement, dated November 2, 2018, by and among the Registrant, Solar Capital Ltd., as collateral agent and lend, and the other lenders named therein	8-K	001-35837	11/5/18	10.1
21.1*	Subsidiaries of the Registrant				
23.1*	Consent of Ernst & Young LLP				
31.1*	Chief Executive Officer—Certification pursuant to Rule 13a-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				
31.2*	Principal Financial Officer—Certification pursuant to Rule 13a-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				

Exhibit Number	Description	Incorporated by Reference from Registrant's Form	File No.	Date Filed with the SEC	Exhibit Number
32.1*	Chief Executive Officer—Certification pursuant to Rule 13a-14(a) of the Securities Exchange Act of 1934 and 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002				
32.2*	Principal Financial Officer—Certification pursuant to Rule 13a-14(a) of the Securities Exchange Act of 1934 and 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002				
101.INS*	XBRL Instance Document				
101.SCH*	XBRL Taxonomy Extension Schema Document				
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document				
101.DEF*	XBRL Taxonomy Extension Definition Linkbase Document				
101.LAB*	XBRL Taxonomy Extension Label Linkbase Document				
101.PRE*	XBRL Taxonomy Extension Presentation Linkbase Document				

*Filed herewith.
#Indicates management contract or compensatory plan or arrangement.
†Confidential treatment requested as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commission.

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.

TETRAPHASE PHARMACEUTICALS, INC.

Date: March 15, 2019 By: /s/ Guy Macdonald
Guy Macdonald

President & 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 and on the dates indicated.

Signature	Title	Date
/s/ Guy Macdonald Guy Macdonald	Director, President and Chief Executive Officer (Principal Executive Officer)	March 15, 2019
/s/ Christopher Watt Christopher Watt	Senior Vice President, Finance (Principal Financial and Accounting Officer)	March 15, 2019
/s/ L. Patrick Gage L. Patrick Gage, Ph.D.	Chairman	March 15, 2019
/s/ Garen Bohlin Garen Bohlin	Director	March 15, 2019
/s/ Jeffrey A. Chodakewitz Jeffrey A. Chodakewitz	Director	March 15, 2019
/s/ John G. Freund John G. Freund	Director	March 15, 2019
/s/ Geraldine Henwood Geraldine Henwood	Director	March 15, 2019
/s/ Nancy Wysenski Nancy Wysenski	Director	March 15, 2019

115