# 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 001-38503**

# Iterum Therapeutics plc

**(Exact name of Registrant as specified in its Charter)**

| **Ireland** | **98-1283148** |
|---|---|
| **(State or other jurisdiction of incorporation or organization)** | **(I.R.S. Employer Identification No.)** |

**Block 2 Floor 3, Harcourt Centre,**
**Harcourt Street,**
**Dublin 2, Ireland**
**(Address of principal executive offices)**

**Not applicable**
**(Zip Code)**

**(+353) 1 903-8920**
**(Registrant's telephone number, including area code)**

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

| Title of each class | Name of each exchange on which registered |
|---|---|
| Ordinary Shares, $0.01 par value per share | The Nasdaq Stock Market LLC |

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 15(d) of the Act. YES ☐ NO ☒

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

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

Indicate by check mark 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, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

| | | | |
|---|---|---|---|
| Large accelerated filer | ☐ | Accelerated filer | ☐ |
| Non-accelerated filer | ☒ | Smaller reporting company | ☒ |
| | | Emerging growth company | ☒ |

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

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES ☐ NO ☒

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant, based on the closing price of the Registrant's ordinary shares, $0.01 par value per share, on the Nasdaq Global Market on June 30, 2018, was $151,081,043.

The number of shares of Registrant's Common Shares outstanding as of February 28, 2019 was 14,367,441.

**DOCUMENTS INCORPORATED BY REFERENCE**

Part III of this Annual Report on Form 10-K incorporates by reference information from the definitive proxy statement for the Registrant's 2019 Annual Meeting of Shareholders, which is expected to be filed with the Securities and Exchange Commission not later than 120 days after the Registrant's fiscal year ended December 31, 2018.

**Table of Contents**

## SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This Annual Report on Form 10-K contains forward-looking statements that involve risks and uncertainties. All statements other than statements of historical facts contained in this Annual Report are forward-looking statements. In some cases, you can identify forward-looking statements by words such as "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "seek," "should," "target," "will," "would," or the negative of these words or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our use of cash reserves;
- the initiation, timing, progress and results of our preclinical studies and clinical trials, and our research and development programs;
- our ability to retain the continued service of our key professionals and to identify, hire and retain additional qualified professionals;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- the potential advantages of our product candidates;
- the timing or likelihood of regulatory filings and approvals;
- the commercialization of our product candidates, if approved;
- our ability to draw down our second term loan with Silicon Valley Bank;
- our manufacturing plans;
- our sales, marketing and distribution capabilities and strategy;
- market acceptance of any product we successfully commercialize;
- the pricing, coverage and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business and product candidates;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates;
- our ability to enter into strategic arrangements, collaborations and/or commercial partnerships in the United States and other territories and the potential benefits of such arrangements;
- our estimates regarding expenses, capital requirements and needs for additional financing;
- our expectations regarding how far into the future our cash on hand will fund our ongoing operations;
- our financial performance; and
- developments relating to our competitors and our industry.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in "Risk Factors" and elsewhere in this Annual Report. Moreover, we operate in a very competitive and rapidly changing environment, and new risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this Annual Report may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this Annual Report to conform these statements to new information, actual results or to changes in our expectations, except as required by law.

You should read this Annual Report and the documents that we have filed with the Securities and Exchange Commission, or SEC, as exhibits to this Annual Report with the understanding that our actual future results, levels of activity, performance, and events and circumstances may be materially different from what we expect.

This Annual Report also contains industry, market and competitive position data from our own internal estimates and research as well as industry and general publications and research surveys and studies conducted by third parties. Industry publications, studies, and surveys generally state that they have been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our internal data and estimates are based upon information obtained from trade and business organizations and other contacts in the markets in which we operate and our management's understanding of industry conditions. While we believe that each of these studies and publications is reliable, we have not independently verified market and industry data from third-party sources. While we believe our internal company research is reliable and the market definitions are appropriate, neither such research nor these definitions have been verified by any independent source. The industry in which we operate is subject to a high degree of uncertainty and risks due to various factors, including those described in the section titled "Risk Factors."

In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this Annual Report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

## PART I

### Item 1. Business.

**Overview**

We are a pharmaceutical company dedicated to developing and commercializing sulopenem to be potentially the first and only oral and intravenous (IV) branded penem available globally. Penems, including thiopenems and carbapenems, belong to a class of antibiotics more broadly defined as ß-lactam antibiotics, the original example of which was penicillin, but which now also includes cephalosporins. Sulopenem is a potent, thiopenem antibiotic delivered intravenously which is active against bacteria that belong to the group of organisms known as gram-negatives and cause urinary tract and intra-abdominal infections. We have also successfully developed sulopenem in an oral tablet formulation, sulopenem etzadroxil-probenecid. Both sulopenem product candidates have the potential to be important new treatment alternatives to address growing concerns related to antibacterial resistance without the known toxicities of some of the most widely used antibiotics, specifically fluoroquinolones. We see two distinct opportunities for our sulopenem program: patients at elevated risk for treatment failure in the community setting suffering from uncomplicated urinary tract infections (uUTI) and hospitalized patients suffering from complicated, antibiotic-resistant infections. During the third quarter of 2018, we initiated all three clinical trials in our Phase 3 development program, which includes: a Phase 3 uncomplicated urinary tract infections, or uUTI, clinical trial, known as SUlopenem for Resistant Enterobacteriaceae (SURE) 1, comparing oral sulopenem to oral ciprofloxacin in women with uUTI, a Phase 3 complicated urinary tract infections, or cUTI, clinical trial known as SURE 2, comparing IV sulopenem followed by oral sulopenem to IV ertapenem followed by oral ciprofloxacin in adults with cUTI, and a Phase 3 complicated intra-abdominal infections, or cIAI, clinical trial known as SURE 3, comparing IV sulopenem followed by oral sulopenem to IV ertapenem followed by a combination of oral ciprofloxacin and oral metronidazole in adults with cIAI. We designed one Phase 3 clinical trial in each indication based on our end of Phase 2 meeting with the U.S. Food and Drug Administration (FDA) and feedback from the European Medicines Agency (EMA). We are conducting these three Phase 3 clinical trials under Special Protocol Assessment (SPA) agreements from the FDA. We expect to complete enrollment and produce top-line data for all three clinical trials in the second half of 2019, and to submit our new drug applications (NDAs) to the FDA by the end of 2019.

In November 2015, we acquired an exclusive, worldwide license under certain patents and know-how to develop and commercialize sulopenem and its oral prodrug, sulopenem etzadroxil, from Pfizer Inc. (Pfizer). Pfizer conducted Phase 1 and Phase 2 clinical trials of sulopenem delivered intravenously in Japan in over 1,450 patients with a variety of hospital and community acquired infections. These clinical trials documented a treatment effect in the indications studied and provided preliminary insights into the safety profile for sulopenem, which will continue to be assessed with additional clinical trials. Pfizer subsequently developed sulopenem into a prodrug formulation, sulopenem etzadroxil, to enable oral delivery. Once this prodrug is absorbed in the gastrointestinal tract, the etzadroxil ester is immediately cleaved off and the active moiety, sulopenem, is released into the bloodstream. We have further enhanced this prodrug formulation with the addition of probenecid to extend sulopenem's half-life and enhance its antibacterial potential. Probenecid is a pharmacokinetic enhancer that has been safely and extensively used globally for decades. The oral dose of sulopenem etzadroxil-probenecid has been combined in a single bilayer tablet, which we refer to as oral sulopenem. We refer to sulopenem delivered intravenously as sulopenem and, together with oral sulopenem, as our sulopenem program.

The treatment of urinary tract and intra-abdominal infections has become more challenging because of the development of resistance by pathogens responsible for these diseases. There are approximately 13.5 million emergency room and office visits for symptoms of urinary tract infections (UTIs) and approximately 21 million uUTIs in the United States annually. Based on market research, physicians estimated that approximately 35% of these patients are at elevated risk for treatment failure. Proper antibiotic treatment of drug-resistant infections in this group is particularly important due to the risks associated with treatment failure. Elevated risk patients were defined in the research as patients with recurrent UTIs, elderly patients, patients who have a suspected or confirmed drug-resistant infection, patients with comorbidities (e.g., Diabetes mellitus) or that are immunocompromised, patients that have had a recent hospitalization, patients with a history of prior antibiotic failure and patients in a long-term care setting. Treatment failures pose significant clinical and economic challenges to the healthcare system. There are also approximately 3.6 million patients with cUTI and approximately 350,000 patients with cIAI that require antibiotic therapy every year in the United States.

Growing antibiotic resistance to *E. coli,* the primary cause of UTIs, has complicated the choice of treatment alternatives in both the community and hospital settings, reducing effective treatment choices for physicians. In addition, the Infectious Diseases Society of America and European Society for Microbiology and Infectious Diseases recommend against empiric use, or prescribing without results from a bacterial culture, of fluoroquinolones for uUTIs in their 2010 Update to the International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women. Similarly, the FDA in its November 2015 Advisory Committee meeting stated that the risk of serious side effects caused by fluoroquinolones generally outweighs the benefits for patients with uUTIs and other uncomplicated infections. Subsequently, the FDA mandated labeling modifications for fluoroquinolone antibiotics directing healthcare professionals to reserve fluoroquinolones for patients with no other treatment alternatives. In December 2018 the FDA further warned that fluoroquinolone antibiotics could cause aortic aneurysm and dissection in certain

patients, especially older persons. In October 2018, the EMA's pharmacovigilance risk assessment committee recommended restrictions on the use of broad-spectrum antibiotics, fluoroquinolones and quinolones, following a review of side effects that were reported to be "disabling and potentially long-lasting" The committee further stated that fluoroquinolones and quinolones should only be used to treat infections where an antibiotic is essential, and others cannot be used.

None of the most commonly used oral antibiotics for treatment of uUTIs were initially approved by the FDA within the last two decades. We believe oral sulopenem will be an important empiric treatment option for elevated risk uUTI patients because of its potency against resistant pathogens, as well as its spectrum of antibacterial activity. In addition, oral sulopenem will allow patients who develop an infection with a resistant pathogen but are stable enough to be treated in the community, to avoid the need for an IV catheter and even hospitalization. The primary endpoint of our uUTI Phase 3 clinical trial is designed to demonstrate non-inferiority in patients with ciprofloxacin-susceptible pathogens but also provides an opportunity to demonstrate superiority to ciprofloxacin for oral sulopenem in patients with ciprofloxacin-resistant pathogens.

In the hospital setting, the lack of effective oral stepdown options results in the potential for lengthy hospital stays or insertion of a peripherally inserted central catheter (PICC) to facilitate administration of IV antibiotics, even for some patients with relatively straightforward infections. Our sulopenem program may enable faster discharges, providing cost-saving advantages for the hospital and mitigating the risk of catheter-related infection for patients. Based on potency, safety and formulation advantages, we believe our sulopenem program is uniquely positioned to address unmet medical needs for patients suffering from uncomplicated and complicated infections in both the community and hospital settings.

If the FDA approves oral sulopenem and sulopenem, we plan to seek a commercial partner and/or build a commercial infrastructure to launch both product candidates in the United States. Data from a study we commissioned in 2017 to quantify quinolone resistance by zip code, in addition to data from our clinical trials and available prescriber data, will inform our initial targeted sales force as to where the medical need for a new, effective therapy for UTIs is highest in the community and hospital settings. Outside of the United States, we are evaluating our options to maximize the value of our sulopenem program.

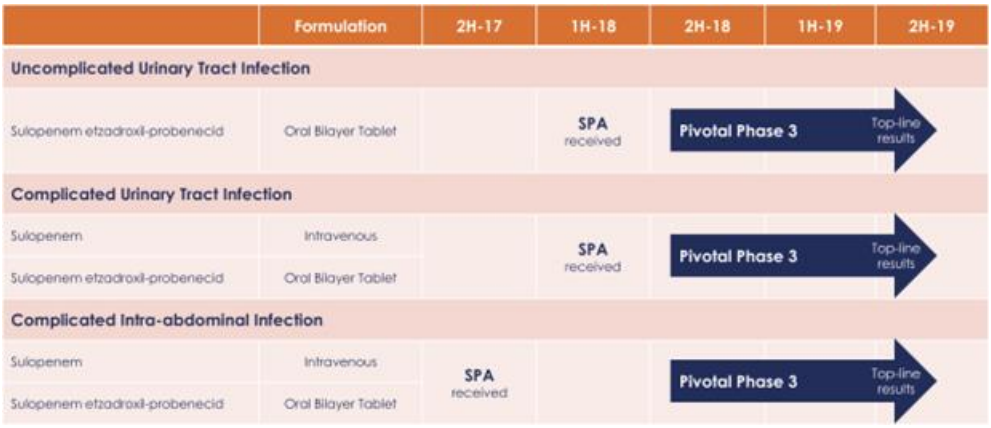
We expect to register two suppliers and validate at least one supplier for the manufacture of the active pharmaceutical ingredient (API) at the time of our planned regulatory filings in the United States by the end of 2019. We will initially rely on a single third-party facility to manufacture all of our sulopenem tablets. In the future, given the importance of oral sulopenem to our potential commercial results, we will consider establishing additional sources.

Sulopenem etzadroxil has an issued composition of matter patent in the United States (which we have exclusively licensed from Pfizer) that is scheduled to expire in 2029, subject to potential extension to 2034 under the Drug Price Competition and Patent Term Restoration Act of 1984, hereinafter referred to as the Hatch-Waxman Act. In addition, the FDA has designated sulopenem and oral sulopenem as Qualified Infectious Disease Products (QIDP) for the indications of uUTI, cUTI, cIAI, community-acquired bacterial pneumonia, acute bacterial prostatitis, gonococcal urethritis, and pelvic inflammatory disease pursuant to the Generating Antibiotic Incentives Now Act (the GAIN Act). Fast track designation for these seven indications in both the oral and intravenous formulations has also been granted. QIDP status makes sulopenem and oral sulopenem eligible to benefit from certain incentives for the development of new antibiotics provided under the GAIN Act. Further, QIDP status could add five years to any regulatory exclusivity period that we may be granted. QIDP status for other indications is also possible given the coverage of gram-negative and gram-positive bacteria by sulopenem, pending submission of additional documentation and acceptance by the FDA. None of our licensed patents cover the IV formulation of sulopenem. Fast track status provides an opportunity for more frequent meetings with the FDA, more frequent written communication related to the clinical trials, eligibility for accelerated approval and priority review and the potential for a rolling review.

**Sulopenem Program, Clinical and Regulatory Status**

We plan to pursue three initial indications for oral sulopenem and sulopenem, as summarized in the chart below. We designed these Phase 3 clinical trials based on extensive *in vitro* microbiologic surveillance data, Phase 1 pharmacokinetic data from healthy volunteers as well as population pharmacokinetic data from patients, animal models in relevant disease settings, Phase 2 data from a program performed with sulopenem by Pfizer in Japan in the early 1990s, and regulatory feedback from the FDA at our end-of-Phase 2 meeting, all supported by an advanced commercial manufacturing program which will provide clinical supplies.

In the third quarter of 2018 we initiated all three Phase 3 clinical trials, which are being conducted under SPA agreements from the FDA. We expect to complete enrollment and produce top-line data for all three clinical trials in the second half of 2019 and submit our NDAs to the FDA by the end of 2019.




**Our Strategy**

Our strategy is to develop and commercialize our sulopenem program for multiple indications, and in the long term to build a market-leading anti-infective business. The key elements of this strategy include the following:

- ***Complete sulopenem clinical development in three initial indications.*** Conduct single Phase 3 clinical trials in each of our three initial indications: uUTI, cUTI and cIAI. All three clinical trials were initiated in the third quarter of 2018, and we expect to conclude enrollment in the second half of 2019, with top-line data available in the same period. Each of these trials is being conducted under a SPA agreement with the FDA.
- ***Obtain regulatory approval for oral sulopenem and sulopenem in the United States and subsequently in the European Union.*** We designed our Phase 3 clinical program based on extensive discussions with the FDA, including our end-of-Phase 2 meeting in July 2017, and considered scientific advice received from the EMA to meet the regulatory filing requirements in the European Union. If our Phase 3 clinical trials are successful, we plan to submit NDAs for both oral sulopenem and sulopenem to the FDA by the end of 2019 and subsequently submit an MAA to the EMA.
- ***Maximize commercial potential of our sulopenem program.*** If approved, we intend to seek a commercial partner and/or directly commercialize our sulopenem program in the United States with a targeted sales force across the community and hospital settings. Outside of the United States, we are evaluating our options to maximize the value of our sulopenem program.
- ***Pursue the development of oral sulopenem and sulopenem in additional indications.*** In the future, we may pursue development of our sulopenem program in additional indications in adults and children, including community acquired bacterial pneumonia, bacterial prostatitis, diabetic foot infection and bone and joint infection, as well as new formulations to support these indications.
- ***Build a portfolio of differentiated anti-infective products.*** We intend to enhance our product pipeline through strategically in-licensing or acquiring clinical stage product candidates or approved products for the community and/or hospital and acute care markets. We believe that our focus on acute care in both the community and hospital markets will make us an attractive partner for companies seeking to out-license products or product candidates in our areas of focus.

***The Medical Need***

*Urinary Tract and Intra-Abdominal Infections*

UTIs are among the most common bacterial infections encountered in the ambulatory setting. A UTI occurs when one or more parts of the urinary system (kidneys, ureters, bladder or urethra) become infected with a pathogen (most frequently, bacteria). While many UTIs are not considered life-threatening, if the infection reaches the kidneys, serious illness, and even death, can occur. UTI diagnoses are stratified between either complicated or uncomplicated infections. uUTI refers to the invasion of a structurally and functionally normal urinary tract by a nonresident infectious organism (e.g., acute cystitis), and is diagnosed and commonly treated in an outpatient setting with an oral agent. Conversely, cUTIs, including acute pyelonephritis, are defined as a UTI ascending from the bladder accompanied by local and systemic signs and symptoms, including fever, chills, malaise, flank pain, back pain, and/or costo-

vertebral angle pain or tenderness, that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization, with treatment typically initiated by IV therapy in a hospital setting.

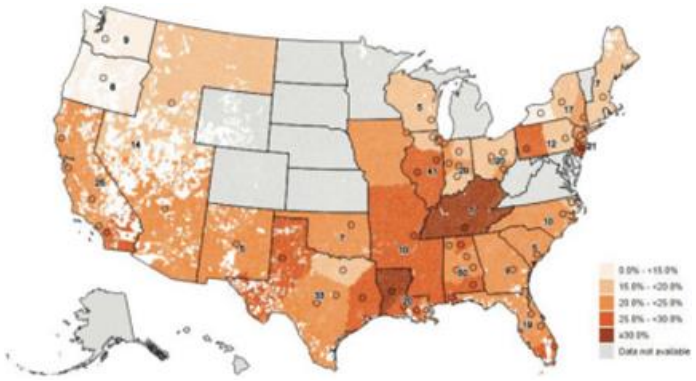
cIAIs have similar challenges to those of cUTIs. These complicated infections extend from a gastrointestinal source, such as the appendix or the colon, into the peritoneal space and can be associated with abscess formation.

*Antimicrobial Resistance is Increasing*

*E. coli* is growing increasingly resistant to many classes of antibiotics, which is especially problematic for patients suffering from UTIs because *E. coli* is the primary cause of those infections. The market-leading antibiotics, fluoroquinolones (e.g., Cipro, Levaquin) and trimethoprim-sulfamethoxazole (e.g., Bactrim, Septra), currently have *E. coli* resistance rates over 20% nationally. In 2015, approximately 75% of oral prescriptions for UTIs written in the United States were for fluoroquinolones or trimethoprim-sulfamethoxazole. In hospitals, fluoroquinolones have greater than 30% resistance to *E. coli* in approximately half the states in the United States, and have greater than 25% resistance rates in nearly 80% of the states. Between 2000 and 2009 the prevalence of extended spectrum ß-lactamases (ESBL)-producing *E. coli* and ESBL-producing *K. pneumoniae* more than doubled from 3.3% to 8.0% and from 9.1% to 18.6%, respectively. During the same timeframe, hospitalizations caused by ESBL-producing organisms increased by about 300%. The national resistance rate of *E. coli* to cephalosporins was estimated to be approximately 13% for the combined years of 2011 to 2015.

We have further delineated the prevalence of bacterial resistance to antibiotics used to treat UTIs in the United States. Based on urine culture results obtained at the zip code level from outpatient UTIs, we concluded that the prevalence of resistance of Enterobacteriaceae to quinolone antibiotics is over 20% in a significant portion of the country. In addition, in 2015, 25 states identified as high prevalence for *E. coli* resistance produced approximately 75% of all UTI prescriptions in the United States.

**Geographic prevalence of quinolone non-susceptible Enterobacteriaceae by zip code in outpatient urine cultures.**




*Numbers represent hospital centers from which data were derived*

As antibiotic resistance leads to increased costs of treatment and increased morbidity, as well as increased mortality, there is an urgent unmet medical need for antimicrobial agents that can be utilized in community and hospital infections. The antimicrobial class of penems has the potential to address many of the relevant resistance issues associated with ß-lactam antibiotics because of a targeted spectrum of antibacterial activity and intrinsic stability against hydrolytic attack by many ß-lactamases, including ESBL and AmpC enzymes.

*There is a Significant Population at Risk*

There are approximately 13.5 million emergency room and office visits for symptoms of UTIs and approximately 21 million uUTIs in the United States annually. Based on market research, physicians estimated that approximately 35% of these patients are at elevated risk for treatment failure. Proper antibiotic treatment of drug-resistant infections in this group is particularly important due to the consequences associated with treatment failure. Elevated risk patients were defined in the research as patients with recurrent UTIs,

elderly patients, patients who have a suspected or confirmed drug-resistant infection, patients with comorbidities (e.g., Diabetes mellitus) or that are immunocompromised, patients that have had a recent hospitalization, patients with a history of prior antibiotic failure and patients in a long-term care setting.

There are also approximately 3.6 million patients with cUTI and approximately 350,000 patients with cIAI that require antibiotic therapy every year in the United States.

*Limited Treatment Options*

In addition to worsening antibiotic resistance, many of the antibiotics currently used for first-line empiric oral treatment of uUTIs, such as nitrofurantoin and trimethoprim-sulfamethoxazole, suffer from significant safety and tolerability concerns. Pulmonary fibrosis and diffuse interstitial pneumonitis has been observed in patients treated with nitrofurantoin, which is contraindicated in pregnant women after 38 weeks of gestation and newborn children due to hemolytic anemia and in patients with poor renal function. Trimethoprim-sulfamethoxazole is associated with fatal hypersensitivity reactions, embryofetal toxicity, hyperkalemia, gastrointestinal disturbances and rashes, including rare cases of Stevens-Johnson Syndrome. In addition, some antibiotics, such as nitrofurantoin and fosfomycin, have poor tissue penetration. While fluoroquinolones are now the most widely used antibiotic class in treating community and hospital gram-negative infections, the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases now recommend against empiric use of fluoroquinolones for uUTIs in their 2010 Update to the International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women as they “have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis.” Similarly, the FDA in its November 2015 Advisory Committee meeting stated that the risk of serious side effects caused by fluoroquinolones generally outweighs the benefits for patients with uUTIs and other uncomplicated infections. Serious side effects associated with fluoroquinolones include tendon rupture, tendinitis, and worsening symptoms of myasthenia gravis and peripheral neuropathy. Subsequently, the FDA mandated labeling modifications for fluoroquinolones antibiotics directing healthcare professionals to reserve fluoroquinolones for patients with no other treatment alternatives. In December 2018 the FDA further warned that fluoroquinolone antibiotics could cause aortic aneurysm and dissection in certain patients, especially older persons. In October 2018 the EMA’s pharmacovigilance risk assessment committee recommended restrictions on the use of broad-specturm antibiotics, fluoroquinolones and quinolones, following a review of side effects that were reported to be “disabling and potentially long-lasting”. The committee further stated that fluoroquinolones and quinolones should only be used to treat infections where an antibiotic is essential, and others cannot be used.

The limited oral antibiotic treatment options for patients with uUTIs can sometimes result in hospitalization to facilitate administration of IV antibiotics for patients whose infection progresses; In addition, some patients whose uUTI remains uncomplicated may require hospital admission for IV therapy. For patients with cUTIs, the lack of effective oral stepdown options, and the paucity of new treatment options, which is demonstrated by the fact that none of the most commonly used oral agents were initially approved by the FDA in the last two decades, results in the potential for lengthy hospital stays or insertion of a PICC to facilitate administration of IV antibiotics, even for some patients with relatively straightforward infections. Therefore, based both on the epidemiology described above and recent discussions with practicing clinicians and pharmacists, we believe there is a pressing need for a novel oral antibacterial therapy for UTI, both complicated and uncomplicated, that has potent activity against ESBL producing and quinolone resistant gram-negative organisms.

*The Challenge of Developing Antibiotics*

Antibiotics work by targeting a critical function of the bacteria and rendering it non-functional. These critical functions include the ability to make proteins, to replicate further, and to build protective envelopes against the harsh external environment. These functions are coded in the bacteria’s DNA, which is copied over to each generation. Occasionally errors are made in the copying; typically, these errors kill off the progeny but can sometimes actually help them survive under specific circumstances, namely when threatened by an antibiotic.

Bacterial mutations, these changes in DNA coding, allow the organism to adapt their protein structures so as to prevent target-specific antibiotics from working. Over time, subsequent generations of bacteria retain these mutations and even develop additional mutations making them resistant to multiple classes of antibiotics and generating what is known as multi-drug resistant (MDR) pathogens. Furthermore, bacteria have also developed mechanisms that allow them to pass these genetic mutations directly to other nearby bacteria, even those from a different species. As there are a limited number of antibiotic classes available today, there is a concern that eventually we will not have any antibiotics to treat patients who develop an infection caused by these MDR bacteria. We continue to need new antibiotics that stay one step ahead of these mutating bacteria in order to protect against the infections that they cause.

*The Solution to Rising Resistance*

The solution to the problem of resistance is based on strategies to use those antibiotics only when patients really need them, limiting the number of opportunities for the bacteria to develop these mutations, and to continue efforts aimed at the discovery and development of new and effective antibacterial agents.

These new agents will need to:

- kill the organisms responsible for the actual infection;
- target a specific bacterial function and overcome the existing resistance mechanisms around that function;
- be powerful enough to require a minimal amount of drug to kill the organism at the site of infection; and
- be delivered to a patient in a manner which is safe, tolerable and convenient.

For the last thirty years, the penem class of antibiotics, including carbapenems such as imipenem, meropenem, doripenem and ertapenem, have been potent and reliable therapeutic options for patients with serious infections. Their spectrum of activity includes those pathogens responsible for infections such as those in the intra-abdominal space, urinary tract, and respiratory tract with a potency as good or better than any other antibiotic class, targeting the cell wall of bacteria, a critical element of bacterial defense. Resistance to the class, generally caused by organisms which have acquired a carbapenemase, is rarely, if ever, seen in the community setting and is primarily localized to patients with substantial healthcare exposures, particularly recent hospitalizations. These drugs are generally very well tolerated. Their limitation is the requirement to be delivered intravenously, restricting their utility to hospitalized patients.

***Our Sulopenem Program***

Our sulopenem program has the potential to offer a solution to the problem of antibiotic resistance and the limitations of existing agents. Sulopenem has *in vitro* activity against gram-negative organisms with resistance to one or more established antibiotics and can be delivered in an oral formulation. If a UTI occurs in the community setting, oral sulopenem can be provided as a tablet, offering an option for care of those with a culture proven or suspected MDR pathogen, potentially avoiding the need for hospitalization. If a patient requires hospitalization for an infection due to a resistant organism, treatment can be initiated intravenously with sulopenem and once the infection begins to improve, stepped down to oral sulopenem, potentially enabling the patient to leave the hospital.

***Potential Advantages of Oral Sulopenem and Sulopenem***

We are developing our sulopenem program to offer patients and clinical care providers a new option to treat drug-resistant gram-negative infections with confidence in its antimicrobial activity, and the flexibility to treat patients in the community while getting those hospitalized back home.

Sulopenem's differentiating characteristics include:

- ***Activity as an oral agent and favorable pharmacokinetic profile.*** Sulopenem is the active moiety with antibacterial activity. Oral sulopenem is a prodrug specifically selected among many other prodrug candidates because it enables the absorption of sulopenem from the gastrointestinal tract. It is this oral agent, sulopenem etzadroxil, combined with probenecid that we believe meets an urgent medical need to allow patients with resistant pathogens to be treated safely in the community, as well as allowing hospitalized patients to continue their treatment at home. Oral sulopenem is sufficiently absorbed from the gastrointestinal tract to allow the parent compound, sulopenem, to achieve adequate exposure in the tissues and, as demonstrated in animal models, to significantly reduce the burden of offending pathogens. Based on pharmacokinetic modeling and supported by prior clinical data from Japan, we believe dosing of the oral agent twice daily will provide tissue exposure sufficient to resolve clinical infection.
- ***Targeted spectrum of activity against relevant pathogens without pressure on other incidental gram-negative organisms.*** Sulopenem is active against the pathogens that are most likely to cause infection of the urinary and gastrointestinal tract, including *E. coli*, *K. pneumoniae*, *P. mirabilis* and *B. fragilis*. Like ertapenem, sulopenem is not active against certain gram-negative organisms such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. These organisms are not typically seen in community UTIs and are infrequently identified in UTIs in the hospital, except when patients have had an indwelling urinary catheter for an extended duration. As a result, we believe the targeted spectrum of sulopenem is less likely to put pressure on those pathogens which could otherwise have led to carbapenem resistance.
- ***Activity against multidrug resistant pathogens.*** Bacteria are accumulating resistance mechanisms to multiple classes of antibiotics within the same organism, and, as a consequence, physicians are losing confidence in existing antibiotics as

empiric therapy before culture results become available. Sulopenem is active against organisms that have multiple resistance mechanisms and can help avoid some of the consequences of ineffective antibiotic therapy.

- ***Documented safety and tolerability profile.*** Adverse event data collected as part of the Japanese Phase 2 development program conducted by Pfizer with the IV formulation provided preliminary insights into the safety profile for sulopenem, which will continue to be assessed with additional clinical trials. Data is also available for the oral formulation collected in healthy volunteers in the Phase 1 program conducted by us that is consistent with a well-tolerated regimen and similar to the adverse event profile observed with the IV formulation. One additional adverse event identified with the oral prodrug is loose stools, which were considered of mild severity and were self-limited, as seen with other broad spectrum oral antibiotics with activity against the anaerobic flora of the gastrointestinal tract. In the Japanese program, one patient reported a serious adverse event related to sulopenem of a transient elevation in liver function tests. The patient died due to metastatic lung cancer. Other serious adverse events recorded in patients receiving sulopenem in the Japanese program, which were not related by the investigator to sulopenem, included myocardial infarction with respiratory failure and progression of underlying ovarian carcinoma, in both cases resulting in death. For each of these patients, sulopenem was not determined to be the cause of death.
- ***Availability of an IV formulation.*** Sulopenem is expected to be available intravenously. Patients sick enough to require hospitalization may not be good candidates for initial oral therapy given potential uncertainties around the ability to absorb drugs due to diminished gastrointestinal and target tissue perfusion in patients with compromised cardiovascular status associated with sepsis or reduced gastrointestinal motility. An IV and oral formulation will enable the conduct of clinical registration trials in a manner consistent with typical clinical practice, allow for confidence in the initiation of therapy in seriously ill patients and, if approved, offer both important formulations as therapeutic options.
- ***Advanced manufacturing program.*** The synthetic pathway for sulopenem, initially defined in the 1980s, has now evolved through its third iteration, incorporating improvements in yield and scalability. We expect to register two different contract manufacturing organizations to manufacture the API for oral sulopenem and sulopenem. Both of the contract manufacturers have the capability to produce vials for IV delivery. We will initially rely on a single third-party facility to manufacture all of our sulopenem tablets. In the future, given the importance of sulopenem to our potential commercial results, we will consider establishing additional sources.

***Market Opportunity for Oral Sulopenem and Sulopenem***

Based upon the clinical evidence to date in eradicating key pathogens, coupled with unmet medical needs, if approved, we expect the commercial opportunity for oral sulopenem and sulopenem to be substantial with initial focus on the following areas:

- treating uUTI with an oral formulation in community treatment settings;
- treating cUTI with initiation of IV therapy in the hospital;
- treating cUTI with an oral formulation upon discharge from hospital to complete therapy in the community setting;
- treating cIAI with initiation of IV therapy in the hospital; and
- treating cIAI with an oral formulation upon discharge from hospital to complete therapy in the community setting.

Acute cystitis remains one of the most common indications for prescribing antimicrobials to otherwise healthy women, resulting in as many as 13.5 million office or emergency room visits in the United States annually, according to a review published in 2015. Up to 50% of all women experience one episode by 32 years of age. In addition, there are approximately 3.6 million patients a year in the United States for the more serious cases of cUTI.

In addition, cIAIs are the second most common cause of infectious mortality in intensive care units. Among approximately 350,000 cIAI patients in the United States each year, broad spectrum antibiotics are generally administered as first line treatment; treatment failure is more common due to the serious nature of these infections.

In the United States, *E. coli* resistance presently exceeds 20% for fluoroquinolones, trimethoprim-sulfamethoxazole and ampicillin. Our market research indicated that physicians identified the lack of effective oral agents for these more difficult drug-resistant infections as a key unmet need in their practice. Physicians are particularly concerned by drug-resistant infections in the 35% of patients considered to be at elevated risk for treatment failure, as they pose significant potential clinical and economic challenges to the healthcare system when initial therapy is unsuccessful.

Given the growing prevalence of bacterial resistance that has rendered existing oral therapies ineffective, coupled with the FDA mandating new safety labeling changes to enhance warnings limiting fluoroquinolone use in uncomplicated infections due to the

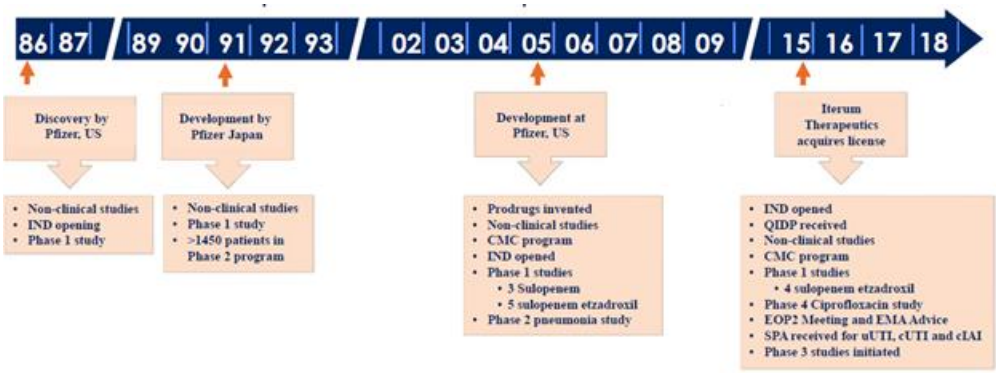
association with disabling and potentially permanent side effects, physicians are seeking new alternatives to safely and effectively treat their patients.

We believe oral sulopenem's value proposition will aid physicians in the community setting to address the unmet need for a safe and effective oral uUTI therapy to treat the growing number of patients with suspected or confirmed resistant pathogen(s). In addition, we believe our sulopenem program will offer a compelling value proposition to hospitals by enabling the transition of patients from IV therapy in the inpatient setting to an oral therapy in the community.

***Oral Sulopenem and Sulopenem Clinical Development Program***

The following graphic provides an overview of the past development of sulopenem etzadroxil and sulopenem by Pfizer and Iterum.

**Discovery, Development, and Regulatory History of Sulopenem and Sulopenem Etzadroxil, by year**




The objective of our sulopenem program is to deliver to patients an oral and IV formulation of sulopenem approved in the United States and Europe for the treatment of infections due to resistant gram-negative pathogens. Sulopenem's spectrum of activity, the availability of an oral agent delivered in a convenient dosing schedule and the evolving safety profile support its further development for the target indications of uUTI, cUTI and cIAI. Oral sulopenem is the oral prodrug metabolized to sulopenem, its therapeutically active form, combined with probenecid.

Both sulopenem and oral sulopenem have received QIDP designation status for the indications of uUTI, cUTI and cIAI as well as for community-acquired bacterial pneumonia, acute bacterial prostatitis, gonococcal urethritis, and pelvic inflammatory disease. Fast track designation for these seven indications in both the oral and intravenous formulations has also been granted. QIDP designation status for other indications is also possible given the coverage of gram-negative and gram-positive bacteria by sulopenem, pending submission of additional documentation and acceptance by the FDA. We have received feedback on the development program in an end of Phase 2 meeting with the FDA, which provided guidance on the size of the safety database, the nonclinical study requirements, the design of the Phase 1 and Phase 3 clinical trials, the pediatric development plan, as well as support for the proposed chemistry, manufacturing and controls (CMC) development activities through production of commercial supplies. The Phase 3 clinical trials for treatment of cIAI, cUTI and uUTI have received SPA agreements with the FDA. All three Phase 3 clinical trials were initiated in the third quarter of 2018, and we expect top-line delivery of data in the second half of 2019 and submission of our NDAs to the FDA by the end of 2019. We also have an agreement with the FDA on a pediatric study plan. Development work on pediatric formulations is ongoing, and we expect to commence Phase 1 studies in children in 2019.

*Microbiology Surveillance Data*

Sulopenem has demonstrated potent *in vitro* activity, as defined by its minimum inhibitory concentration (MIC), against nearly all genera of Enterobacteriaceae, in anaerobes such as Bacteroides, Prevotella, Porphyromonas, Fusobacterium and Peptostreptococcus, gram-positive organisms including methicillin-susceptible staphylococci, *Streptococcus pyogenes* and *Streptococcus pneumoniae*, as well as other community respiratory pathogens such as *Haemophilus influenzae* and *Moraxella catarrhalis*. The MIC is a measure used to describe the results of an *in vitro* assay in which a fixed number of a strain of bacteria are added to a 96-well plate and increasing concentrations of antibiotic are sequentially added to the wells. The concentration of antibiotic which inhibits growth of the bacteria in a well is considered the MIC. When looking across a collection of many strains of a species of

bacteria, the $MIC_{90}$ is the lowest concentration of antibiotic at which 90% of the strains are inhibited Sulopenem lacks *in vitro* activity ($MIC_{90} \geq 16$ µg/mL) against the oxidative non-fermenting pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia.* Given its lack of potency against *Pseudomonas aeruginosa*, its use in treatment of infections caused by pathogenic Enterobacteriaceae should not select for pseudomonas resistant to carbapenems, as can occur with imipenem and meropenem. For various species of enterococci, the $MIC_{90}$ values were 4 to $\geq 64$ µg/mL. Methicillin-resistant staphylococci also have high MIC values.

The table below highlights the $MIC_{50}$ and $MIC_{90}$ of key target pathogens collected by International Health Management Associates (IHMA) between 2013 and 2015 responsible for the infections that will be studied in our Phase 3 program.

| Organism Class | N | $MIC_{50}$ (µg/mL) | $MIC_{90}$ (µg/mL) |
|---|---|---|---|
| *E. coli* | 189 | 0.015 | 0.03 |
| ESBL negative | 169 | 0.015 | 0.03 |
| ESBL positive | 20 | 0.03 | 0.06 |
| *Klebsiella spp.* | 124 | 0.03 | 0.06 |
| ESBL negative | 108 | 0.03 | 0.06 |
| ESBL positive | 16 | 0.03 | 0.25 |
| *P. mirabilis* | 14 | 0.12 | 0.25 |
| *E. aerogenes* | 57 | 0.06 | 0.25 |
| *C. koseri* | 60 | 0.03 | 0.03 |
| *S. marcescens* | 55 | 0.12 | 0.50 |
| Gram-negative anaerobes | 125 | 0.12 | 0.25 |
| *Staphylococcus saprophyticus* | 31 | 0.25 | 0.25 |

A comparison of the *in vitro* activity of sulopenem relative to other carbapenems, as well as to currently prescribed oral agents for UTI, is provided below. The activity of sulopenem at slightly higher doses was very similar to that of ertapenem and meropenem, which are currently commercially available. In addition, sulopenem is noted to have potent *in vitro* activity against relevant organisms that are resistant to fluoroquinolones and trimethoprim-sulfamethoxazole and are ESBL positive. The prevalence of resistance for the existing generic antibiotics, now exceeding 20% for many pathogens, underscores the challenge of treating patients with uUTI in an outpatient setting or releasing patients from the hospital with a cUTI or cIAI on a reliable stepdown oral therapy.

| | ***E. coli*** **N=189** | | ***K. pneumoniae*** **N=65** | | ***P. mirabilis*** **N=19** | |
|---|---|---|---|---|---|---|
| **Penem Class:** | **$MIC_{90}$ (µg/mL)** | **% S** | **$MIC_{90}$ (µg/mL)** | **% S** | **$MIC_{90}$ (µg/mL)** | **% S** |
| **Sulopenem** | **0.06** | * | **0.12** | * | **0.25** | * |
| Ertapenem | 0.015 | 100 | 0.12 | 97 | 0.03 | 100 |
| Meropenem | 0.03 | 100 | 0.06 | 97 | 0.12 | 100 |
| **Oral Agents Currently on Market:** | | | | | | |
| Nitrofurantoin | 16 | 97 | ≥64 | 23 | ≥64 | 0 |
| Fosfomycin | 8 | 98 | 128 | 86 | 64 | 95 |
| Ciprofloxacin | ≥2 | 77 | 1 | 91 | ≥2 | 74 |
| Trimethoprim-Sulfamethoxazole | ≥32 | 74 | ≥32 | 86 | ≥32 | 58 |
| Amoxicillin-Clavulanate | 16 | 76 | ≥16 | 80 | ≥16 | 74 |

N = bacterial samples; each product candidate was tested using the same sample size

% S = percentage susceptible, meaning the proportion of the number of isolates tested that had a MIC below the FDA defined susceptibility breakpoint; boxed values signify a percentage susceptible below 80%, which is the threshold for concern for use of an antibiotic before a culture is available

* Susceptibility breakpoints are established by the FDA and documented in product labeling based on the antibacterial agent treatment efficacy in Phase 3 clinical trials associated with a specific MIC. As such, susceptibility breakpoints have not yet been determined for sulopenem.

*Animal Models*

Sulopenem reduced the bacterial burden in the bladder and tissues of infected animals in a uUTI model in both diabetic and normal C3H/HeN mice using a MDR ST131 *E. coli*, a strain which is ESBL positive and resistant to fluoroquinolones and

trimethoprim-sulfamethoxazole. Sulopenem was highly efficacious and remarkably robust in its reduction in bacterial burden, leading to complete resolution of bacteriuria in all or most of the animals in both study arms with the high dose treatment regimen also reducing bacterial burden in bladder tissue and the kidney.

*Non-clinical Pharmacology*

Metabolic clearance is primarily characterized by hydrolysis of the ß-lactam ring. Sulopenem does not inhibit the major cytochrome P450 isoforms suggesting a low potential for drug interactions at therapeutic concentrations. It is predominantly excreted in the urine. Plasma protein binding for sulopenem is low at approximately 11%.

*Phase 1 Program*

The table below outlines the Phase 1 clinical trials that have been conducted with sulopenem etzadroxil and sulopenem.

| Protocol | Year | Dose (mg), other medication | Subjects on sulopenem or sulopenem etzadroxil | Treatment (Days) |
|---|---|---|---|---|
| **Sulopenem (CP-70,429)—Phase 1 Single Dose Clinical Trials** | | | | |
| A109001 | 1987 | 1000 mg | 6 | 1 |
| Japanese PK | | 250 mg, 500 mg, 1000 mg | 18 | 1 |
| A7371007 | 2007 | 400 mg, 800 mg, 1600 mg, 2400 mg, 2800 mg, placebo | 24 | 1 |
| | 2018 | 366 mg IV, 1000 mg | | |
| IT001-105 (1) | | IV | 46 | 1 |
| **Sulopenem (CP-70,429)—Phase 1 Multiple Dose Clinical Trials** | | | | |
| Japanese PK | | 500 mg, 1000 mg | 12 | 5 |
| Japanese PK | | 1000 mg | 6 | 5 |
| A1091001 | 2009 | 800 mg, 1200 mg, 1600 mg, 2000 mg, placebo | 40 | 14 |
| **Sulopenem etzadroxil (PF-03709270)—Phase 1 Single Dose Clinical Trials** | | | | |
| A8811001 | 2007 | 400 mg, 600 mg, 1000 mg, 2000 mg, placebo | 9 | 1 |
| A8811006 | 2008 | 2000 mg | 4 | 1 |
| A8811007 | 2007 | 600 mg, probenecid | 4 | 1 |
| A8811008 | 2008 | 1200 mg, probenecid | 24 | 1 |
| A8811018 | 2008 | 1000 mg, 1200 mg, probenecid, aluminum hydroxide, pantoprazole | 17 | 1 |
| A8811003 | 2008 | 2000 mg, 4000 mg, 6000 mg, 8000 mg, placebo | 11 | 1 |
| IT001-101 | 2017 | 500 mg, 1000 mg, probenecid | 48 | 1 |
| IT001-102(1) | 2017 | 500 mg, probenecid | 13 | 1 |
| IT001-105 (1) | 2018 | 500 mg, probenecid, bilayer tablet | 36 | 1 |
| **Sulopenem etzadroxil (PF-03709270)—Phase 1 Multiple Dose Clinical Trials** | | | | |
| A8811003 | 2008 | 2000 mg, 1200 mg, probenecid, placebo | 18 | 10 |
| A8811015 | 2009 | 500 mg, 1000 mg, 1500 mg, probenecid, placebo, Augmentin | 48 | 7 |
| IT001-101 | 2017 | 500 mg, probenecid | 64 | 7 |
| **Sulopenem (CP-70,429), Sulopenem etzadroxil (PF-03709270)—Phase 1 Renal Impairment Clinical Trial** | | | | |
| A8811009 | 2010 | 200mg, 800 mg sulopenem or 1000 mg sulopenem etzadroxil | 29 | 1 |
| | | Total | 306 | |

(1) Final report pending.

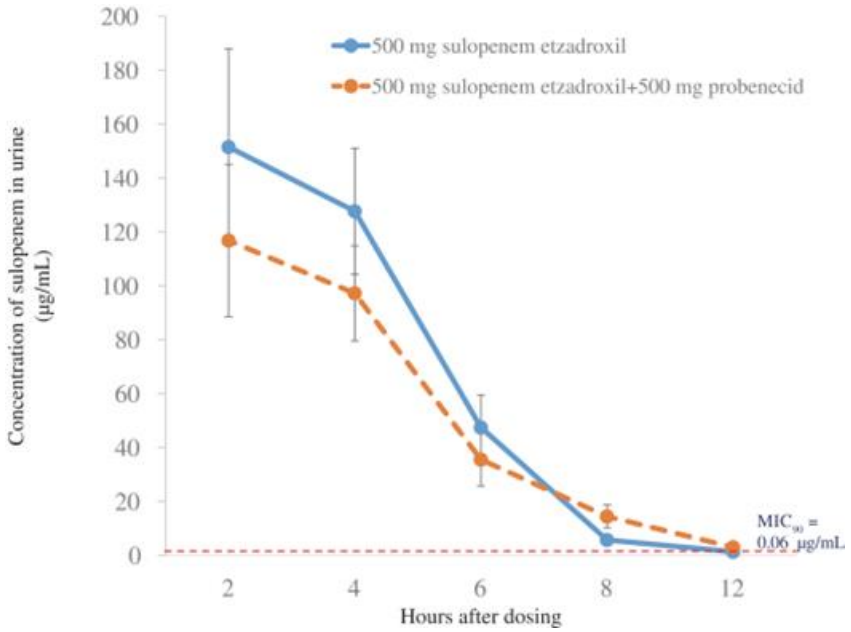
*Oral Sulopenem*

We have designed oral sulopenem to include probenecid, a pharmacokinetic enhancer that delays the excretion through the kidneys of sulopenem and other ß-lactam antibiotics and has been extensively used for this purpose and the treatment of gout. It enables us to maximize the antibacterial potential of any given dose of oral sulopenem.

We conducted three Phase 1 clinical trials, IT001-101, IT001-102 and IT001-105, in healthy volunteers, in part to select the prodrug and explore various doses of probenecid combined with 500 mg of sulopenem etzadroxil. Findings from these clinical trials are consistent with those from other pharmacokinetic studies that employed different total doses of sulopenem etzadroxil. Specifically, the AUC (area under the curve, a measure of total exposure) and Cmax (maximum plasma concentration) are generally dose-proportional, and the concomitant use of probenecid increases the plasma exposure of sulopenem with any dose with which it was studied.

The mean total sulopenem exposures in the urine after a single 500 mg dose in IT001-101 exceeded the $MIC_{90}$ for the entire twice-daily dosing interval in the 32 healthy volunteers who received 500 mg of sulopenem etzadroxil, as illustrated in the graph below. In a urine antibacterial assay, urine collected at two hours post-dose was bactericidal for numerous strains of *E. coli* and *K. pneumoniae*, including a strain of *K. pneumoniae* that was resistant to meropenem and imipenem, with a sulopenem MIC of 16 µg/mL.

**Mean total sulopenem exposure in urine after single 500 mg dose of sulopenem etzadroxil with or without probenecid**




In IT001-102, we evaluated sulopenem etzadroxil administered with and without probenecid in a randomized cross-over trial in healthy volunteers in a fasted state. Subjects receiving sulopenem etzadroxil co-administered with probenecid demonstrated an increase in the time over MIC (of a 12 hour dosing interval) and AUC of sulopenem, as shown in the table below.

| | | | Sulopenem Parameter (Day 1) | | | |
|---|---|---|---|---|---|---|
| **Treatment** | **N** | **Descriptive Statistic** | **$C_{max}$ (ng/mL)** | **$AUC_{0-¥}$ (hr*ng/mL)** | **T>MIC (0.5 µg/mL) [hr]** | **T>MIC (0.5 µg/mL) [%]** |
| **500 mg Sulopenem etzadroxil** | 10 | Mean | 1928 | 3871 | 2.8 | 23.3 |
| **500 mg Sulopenem etzadroxil + 500 mg probenecid** | 11 | Mean | 1929 | 4964 | 3.6 | 30.2 |

N = number of subjects; $C_{max}$ = maximum plasma concentration; $AUC_{0-¥}$ = area under the curve from the initiation of dosing extrapolated through infinite time

In addition, results from IT001-101 demonstrated that food increases the mean AUC and mean time over MIC (0.5 µg/mL) of 500 mg sulopenem etzadroxil dosed with 500 mg probenecid on Day 1 by 62% and 68%, respectively.

A Phase 1 drug interaction study with itraconazole is underway and we plan to conduct an additional drug interaction study with valproic acid to support our NDAs. Other Phase 1 clinical trials may be added as the needs of the program dictate.

*Sulopenem, IV Formulation*

Doses of sulopenem up to 2800 mg as a single IV dose and 2000 mg BID, or twice daily, of sulopenem as IV over fourteen days were studied in three Phase 1 clinical trials in healthy adults, one study in patients with renal insufficiency in the United States and two Phase 1 clinical trials in Japan. Results from these pharmacokinetic studies with various IV doses of sulopenem delivered over various durations established dose proportionality among the regimens with regard to AUC and maximal plasma concentrations ($C_{max}$). A representative analysis of pharmacokinetic parameters, a subset of study A1091001, is described in the table below.

| | N | Dose (mg) | Infusion duration (h) | $C_{max}$ (µg/mL) | AUC $_{0-\infty}$ (µg hr/mL) | $T_{1/2}$ (h) | $CL_{total}$ (mL/min/kg) |
|---|---|---|---|---|---|---|---|
| Day 1 | 8 | 800 | 3 | 7.27 | 22.4 | 0.83 | |
| | 8 | 1200 | 1 | 32.5 | 42.3 | 1.04 | |
| | 8 | 1200 | 2.5 | 16.6 | 41.9 | 1.12 | |
| Day 14 | 5 | 800 | 3 | 8.97 | 26.5 | 0.89 | 15.4 |
| | 6 | 1200 | 1 | 30.7 | 41.4 | 1.05 | 14.7 |
| | 6 | 1200 | 2.5 | 13.5 | 34.6 | 1.01 | 18.8 |

N = number of subjects; $C_{max}$ = maximum plasma concentration; AUC $_{0-\infty}$ = area under the curve from the initiation of dosing extrapolated through infinite time; $T_{½}$ = half-life; $CL_{total}$ = clearance (only measured on Day 14)

*Modeling and Dose Selection*

Based on *in vitro* susceptibility data from surveillance studies, pharmacokinetics gathered from Phase 1 clinical trials, and population pharmacokinetic data from patients, we performed modeling to help choose the doses for the Phase 3 program. The $MIC_{90}$ for all Enterobacteriaceae potentially involved in the target indications was 0.25 µg/mL and for the weighted distribution of pathogens most likely to be associated with the indication was 0.06 µg/mL. We have performed modeling both for the weighted distribution of MICs expected in the clinical trials as well as at a fixed MIC of 0.5 µg/mL. Data obtained from animal experiments confirmed that, similar to carbapenems and lower than that for other ß-lactams, the $\%T_{free}$ >MIC required for bacteriostasis is approximately 10–19%, depending on the dosing regimen; we have used 17% in our models. Based on the outputs from those models, the IV dose of sulopenem being studied in the ongoing Phase 3 clinical trials is 1000 mg sulopenem delivered over 3 hours once a day. The oral dose being studied is 500 mg of sulopenem etzadroxil given with 500 mg of probenecid in a single bilayer tablet twice daily.

*Japanese Clinical Data*

Pfizer's affiliate in Japan conducted extensive clinical development of sulopenem in over 1,450 patients in Phase 1 and Phase 2 clinical trials in Japan in patients with skin infections, respiratory tract infections, gynecologic infections, cUTI and intra-abdominal infections.

**Phase 2 clinical trials conducted by Pfizer in Japan, 1991-1993**

| Study # | Description | Sulopenem Dose | Comparator | N |
|---|---|---|---|---|
| 91-002 | Multiple infections in:<br>Internal medicine<br>Surgery: includes cIAI<br>Urology: pyelonephritis cystitis | 250 mg IV BID<br>500 mg IV BID | None | 108 |
| 92-002 | Multiple infections in:<br>Internal medicine<br>Surgery: includes cIAI<br>Urology: pyelonephritis cystitis | 250 mg IV BID<br>500 mg IV BID | None | 961 |
| 91-002<br>92-002 | Population-Pharmacokinetics (only) | 250 mg IV BID<br>500 mg IV BID | N/A | 216 |
| 93-001 | Respiratory Tract Infection | 250 mg IV BID<br>500 mg IV BID | Cefotiam IV | 75 |

| Study # | Description | Sulopenem Dose | Comparator | N |
|---|---|---|---|---|
| 93-002 | cUTI | 250 mg IV BID<br>500 mg IV BID | Imipenem IV | 114 |
| **Total** | | | | **1474** |

A treatment effect in small Phase 2 clinical trials was observed in a number of infections includingskin infections, respiratory tract infections, gynecologic infections and, most relevant to the targeted indications being pursued in our Phase 3 program, cUTI and cIAI. The data from these clinical trials may not be directly comparable to data from clinical trials that would be conducted today or the data that we anticipate from our Phase 3 program for a variety of reasons, including that the protocols were designed for different purposes and as a consequence had different enrollment and efficacy evaluation criteria. While these data are not required for approval of our intended indications, we believe these results support our decision to develop sulopenem for our targeted indications and informed our dose selection.

In 1993, Pfizer Japan conducted 93-002, a randomized clinical trial in subjects with cUTI, comparing 250 mg twice daily and 500 mg twice daily of sulopenem administered intravenously to an intravenously-delivered imipenem-cilastatin, also given twice daily.

The trial enrolled patients who were hospitalized, with an underlying disease of the urinary tract and with evidence of pyuria, measured by ≥ 5 WBC/hpf (white blood cells per high power field, a measure of inflammation in the urinary tract) at baseline. Study therapy was administered for five days and was open-label with respect to sulopenem versus the comparator but was blinded as to the sulopenem dose. Efficacy was assessed by the investigator based on subjective and objective criteria, as shown below.

The criteria for patient enrollment in the Phase 2 clinical trial 93-002 are different than those currently established by the FDA in guidelines for Phase 3 cUTI registrational trials published in 2015. In addition to an Intent-to-Treat (ITT) analysis, which includes all randomized patients, of the investigator's assessment of overall efficacy based on the original inclusion criteria, a *post hoc* analysis was also performed by Iterum of the investigator's assessment of overall efficacy in the population of patients that met enrollment criteria consistent with current FDA guidance, such as baseline urinalysis with >10 WBC/hpf and a urine culture which grew $>10^5$ susceptible organisms, as shown below. ITT analyses are performed in the population of all randomized patients. Success, as determined by the investigator and specified in the protocol, was judged for each patient based on resolution of symptoms, pyuria and bacteriuria.

| **Investigator Assessment of Overall Efficacy** | **Sulopenem (CP 70,429) 250 mg BID IV n/N (%)** | **Sulopenem (CP 70,429) 500 mg BID IV n/N (%)** | **Comparator n/N (%)** |
|---|---|---|---|
| ITT | | | |
| Success | 33/36 (91.7) | 36/38 (94.7) | 32/39 (82.1) |
| Failure | 2/36 (5.6) | 2/38 (5.3) | 2/39 (5.1) |
| Indeterminant | 1/36 (2.8) | 0 | 5/39 (12.8) |
| Difference vs. comparator (95% CI) | 9.6 (-6.6, 25.9) | 12.7 (-2.1, 28.4) | |
| Clinically Evaluable using FDA inclusion criteria (*post hoc*) | | | |
| Success | 19/20 (95.0) | 22/22 (100.0) | 16/16 (100.0) |
| Failure | 1/20 (5.0) | 0 | 0 |
| Difference vs. comparator (95% CI) | -5.0 (-24.0, 15.3) | 0 (-15.2, 19.8) | |

One patient received a dose other than 250 mg or 500 mg IV BID.

The results of a subset analysis that included patients from clinical trials conducted in 1991 and 1992, 91-002 and 92-002, with a diagnosis that fit the FDA's definition of cIAIs are provided below, based on the investigator's assessment of clinical response at the end of therapy in the ITT and clinically evaluable populations. Success, as determined by the investigator and specified in the protocol, was judged for each patient based on resolution of cIAI signs and symptoms and improvement in relevant laboratory tests.

| **Investigator Assessment of Outcome** | **Sulopenem (CP 70,429) 250 mg BID IV n/N (%)** | **Sulopenem (CP 70,429) 500 mg BID IV n/N (%)** |
|---|---|---|
| ITT | | |
| Success | 14/15 (93.3) | 78/88 (88.6) |
| Failure | 1/15 (6.7) | 4/88 (4.5) |

| Investigator Assessment of Outcome | Sulopenem (CP 70,429) 250 mg BID IV n/N (%) | Sulopenem (CP 70,429) 500 mg BID IV n/N (%) |
|---|---|---|
| Indeterminant | | 6/88 (6.8) |
| Clinically Evaluable | | |
| Success | 14/15 (93.3) | 77/81 (95.1) |
| Failure | 1/15 (6.7) | 4/81 (4.9) |

Three patients received a dose other than 250 mg or 500 mg IV BID.

We used the data collected in these studies to inform the design of the cUTI proposed regimens.

The results of a Phase 2 clinical trial conducted in 1993 in hospitalized patients with community acquired pneumonia (CAP), 93-001, are provided below, including the investigator's assessment of clinical response at the end of therapy in the ITT and clinically and bacteriologically evaluable populations with the bacteriologically evaluable population meaning the clinically evaluable patients who had a baseline pathogen and follow up microbiology data to allow an assessment of bacteriological efficacy. Success, as determined by the investigator and specified in the protocol, was judged for each patient based on resolution of the signs and symptoms of pneumonia, and improvement in radiologic findings and other relevant tests.

| Investigator Response at End of Treatment | Sulopenem CP 70,429 250 mg BID IV n/N (%) | Sulopenem CP 70,429 500 mg BID IV n/N (%) | Comparator n/N (%) |
|---|---|---|---|
| ITT | | | |
| Success | 19/26 (73.1) | 17/23 (73.9) | 22/25 (88.0) |
| Failure | 4/26 (15.4) | 3/23 (13.0) | 2/25 (8.0) |
| Indeterminant | 3/26 (11.5) | 3/23 (13.0) | 1/25 (4.0) |
| Difference vs. comparator (95% CI) | -14.9 (-36.7, 7.7) | -14.1 (-37.1, 8.8) | |
| Clinically Evaluable | | | |
| Success | 18/20 (90.0) | 15/17 (88.2) | 20/20 (100.0) |
| Failure | 2/20 (10.0) | 2/17 (11.8) | |
| Difference vs. comparator (95% CI) | -10.0 (-30.4, 7.3) | -11.8 (-34.7, 5.8) | |
| Bacteriologically Evaluable | | | |
| Success | 8/8 (100.0) | 5/6 (83.3) | 9/9 (100.0) |
| Failure | — | 1/6 (16.7) | — |
| Difference vs. comparator (95% CI) | 0.0 (-33.8, 31.2) | -16.7 (-57.6, 18.1) | |

*Phase 2 Clinical Trial with sulopenem and sulopenem etzadroxil*

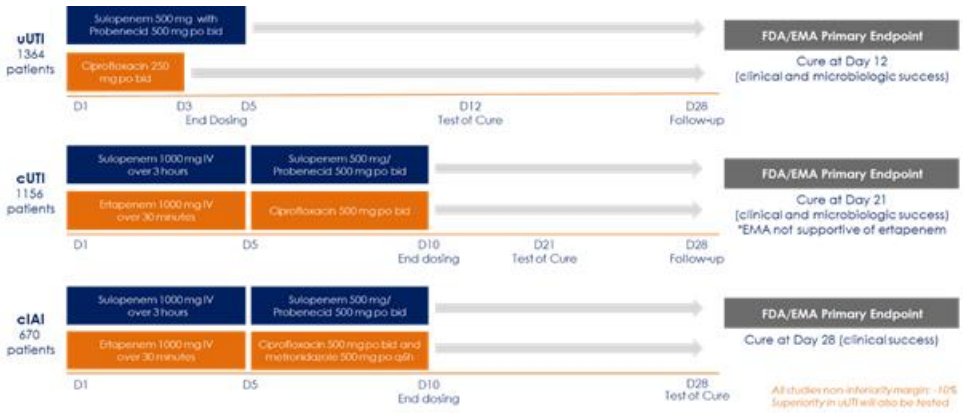
In 2009, Pfizer initiated a Phase 2, randomized, double-blind, double-dummy clinical trial in hospitalized patients with CAP comparing two regimens of IV sulopenem followed by sulopenem etzadroxil to ceftriaxone IV followed by amoxicillin-clavulanate. The sulopenem regimens were a single 600 mg IV dose of sulopenem followed by 1000 mg BID of sulopenem etzadroxil or a 600 mg of sulopenem for a minimum of four doses followed by 1000 mg BID of sulopenem etzadroxil. The clinical trial was terminated early for business reasons after 33 of 250 planned total patients were enrolled and treated. Clinical response rates at the test-of-cure visit (7–14 days after end of therapy) of the ITT patients were similar on each regimen (9/10, 9/11 and 7/12, on sulopenem single IV dose, sulopenem multidose IV and ceftriaxone, respectively). Treatment-emergent adverse events were reported in six subjects each in the sulopenem groups and eight subjects in the ceftriaxone group. The most common treatment-emergent adverse event was diarrhea, reported by a total of six subjects (two in each treatment group). Treatment related diarrhea was reported by one subject following sulopenem single dose IV, and by a further two subjects following ceftriaxone. There was one treatment-related serious adverse event in the ceftriaxone group. There were no deaths reported in this clinical trial.

*Phase 3 Clinical Trials*

Based on FDA Guidance from February 2015 (Complicated Intra-Abdominal Infections: Developing Drugs for Treatment. Guidance for Industry; Complicated Urinary Tract Infections: Developing Drugs for Treatment. Guidance for Industry) and on recently conducted studies by other sponsors, we negotiated SPA agreements for cUTI, cIAI and uUTI. All three Phase 3 clinical trials were initiated in the third quarter of 2018. Oral sulopenem alone is being studied for the treatment of outpatients with uUTI, while oral sulopenem and sulopenem are being studied for the treatment of cUTI and cIAI. A brief overview of the comparator agents, sample size, timing of efficacy assessments and duration of oral and IV dosing is provided in the graphic below. Non-inferiority in these clinical trials is defined by the lower limit of the confidence interval in the treatment difference of no more than -10%. The uUTI clinical trial will also test for superiority in the subset of patients with ciprofloxacin resistant pathogens at baseline. An open-label

noncomparative treatment study of oral ciprofloxacin 250 mg twice daily for three days in uUTI patients was conducted to help characterize certain sample size assumptions as well as enable study logistics for this Phase 3 clinical trial. Patients in the cUTI and cIAI clinical trials will receive five days of sulopenem IV or comparator and then step down to two to five additional days of oral treatment with either oral sulopenem or ciprofloxacin. In the cIAI trial, clinical outcome at the test-of-cure visit will be noted as cure for those patients who are alive, have resolution in signs and symptoms of the index infection and for whom no new antibiotics or interventions for treatment failure were required. In the uUTI and cUTI trials, clinical outcome at the test-of-cure visit will be noted as cure for patients who are alive and who demonstrate resolution of the symptoms of uUTI or cUTI, as applicable, present at trial entry (and no new symptoms) such that no new antibiotics are required, as well as the demonstration that the bacterial pathogen(s) found at trial entry are reduced to $<10^3$ CFU/mL on urine culture on Day 12 or Day 21, respectively.

Patients with an organism resistant to ciprofloxacin in the cUTI and cIAI clinical trials will be allowed to substitute amoxicillin-clavulanate for the stepdown oral therapy. Patients getting ciprofloxacin in the cIAI trial will also receive metronidazole. Patients receiving oral sulopenem will be encouraged, but not required, to dose with food.




*Safety Profile of Oral Sulopenem and Sulopenem*

Sulopenem is a thiopenem and a member of the class of ß-lactam antibiotics, a class from which numerous safe and well tolerated antibiotics have been available for over thirty years. Adverse event data collected as part of the Japanese Phase 2 development program with the IV formulation conducted by Pfizer provided preliminary insights into the safety profile for sulopenem, which will continue to be assessed with additional clinical trials. We view the clinical safety profile of sulopenem established by the Japanese data as also relevant and supportive of oral sulopenem because it metabolizes to the active metabolite, sulopenem, in plasma. A summary of the adverse event data from the Japanese program is provided below:

| | Sulopenem | | | | |
|---|---|---|---|---|---|
| | **250 mg BID (N = 296)** | **500 mg BID (N = 867)** | **Miscellaneous* (N = 247)** | **Comparators (N = 64)** | **Total (N = 1474)** |
| No. of patients who experienced at least one: | | | | | |
| Adverse Event | 14 (4.7) | 35 (4.0) | 1 (0.4) | 3 (4.7) | 53 (3.6) |
| Drug-Related Adverse Event | 9 (3.0) | 22 (2.5) | 1 (0.4) | 3 (4.7) | 35 (2.4) |
| Serious Adverse Event | 2 (0.7) | 1 (0.1) | — | 1 (1.6) | 4 (0.3) |
| Drug-Related Serious Adverse Event | 1 (0.3) | — | — | 1 (1.6) | 2 (0.1) |
| SAE Leading to Death | 2 (0.7) | 1 (0.1) | — | 1 (1.6) | 4 (0.3) |
| AE Leading to Premature Discontinuation of Study Drug | 8 (2.7) | 16 (1.8) | — | 2 (3.1) | 26 (1.8) |
| SAE Leading to Premature Discontinuation of Study Drug | 1 (0.3) | — | — | — | 1 (0.1) |

* Miscellaneous doses include patients receiving a total daily dose of 250 mg, 750 mg, 1500 mg or 2000 mg, including patients receiving a single dose of sulopenem in the population PK sub-study.

Common adverse events occurring in more than one patient on a sulopenem regimen included diarrhea (0.7%), pyrexia (0.5%) and rash (1.0%). The most common adverse event leading to discontinuation was rash (0.7%). Clinically significant laboratory test abnormalities were infrequent. Elevations in serum aminotransferases occurred in approximately 4% of patients.

Data is also available for the oral formulation collected in healthy volunteers in the Phase 1 program conducted by Pfizer and Iterum that is consistent with the adverse event profile observed with the IV formulation. One additional adverse event of interest identified with the oral prodrug, as further assessed in detail in clinical trial IT001-101, is loose stool/diarrhea which was considered of mild severity and self-limited, as seen with other broad spectrum oral antibiotics with activity against the anaerobic flora of the gastrointestinal tract. During the seven-day dosing interval, the incidence of diarrhea, defined as having three or more episodes of loose stool in one day or having two or more episodes of loose stool per day for two consecutive days, peaked at 13% on Day 3 and fell to 2% by Day 7, with no patient discontinuing their dosing due to this event. For patients who took their dose with food, the peak incidence was 9%, dropping again to 3% by Day 4, similar to placebo. Some patients also identified a mild change in the odor of their urine after dosing with either the oral or IV formulations, as can be seen with other ß-lactam antibiotics.

We have received a waiver from the FDA for the requirement of performing a thorough QT interval study given the lack both of any significant preclinical findings and signals in Phase 1 clinical trials during which intensive electrocardiogram monitoring was performed. The EMA in written scientific advice also agreed that a QT interval study is not warranted. A preclinical study of the hydrolysis product of etzadroxil (2-ethylbutyric acid) has been performed in which no effect on plasma carnitine in rats was identified, while a significant effect of a different prodrug moiety, pivoxil, was observed. No reports of seizures, seen with some members of the carbapenem class, were noted in preclinical studies or clinical trials.

**Pfizer License Agreement**

In November 2015, we and our wholly owned subsidiary, Iterum Therapeutics International Limited, entered into a license agreement with Pfizer (the Pfizer License), pursuant to which we acquired from Pfizer an exclusive, royalty-bearing license under certain patent rights and know-how to develop, manufacture and commercialize sulopenem and related compounds, including, among others, sulopenem etzadroxil and three other sulopenem prodrugs, globally for the treatment, diagnosis and prevention of infectious diseases and infections in humans. The licensed patents include two U.S. patents, one of which covers the composition of matter of sulopenem etzadroxil, one patent in Japan, one patent in Hong Kong and one patent in Mexico. None of the licensed patents cover the IV formulation of sulopenem. All patents directed to the compound sulopenem expired prior to us entering into the Pfizer License. Pursuant to the Pfizer License, our exclusive license from Pfizer includes certain know-how, data and regulatory documents that will support the development of sulopenem. We have the right to grant development or commercialization sublicenses to third parties, provided that we (1) obtain Pfizer's prior written consent in connection with such sublicense, (2) enter into a written sublicense agreement consistent with the terms and conditions of the Pfizer License and (3) include Pfizer as a third-party beneficiary under such sublicense. As between Pfizer and us, we own all right, title and interest in any intellectual property rights that are developed by us or our sublicensees in connection with the Pfizer License.

Under the Pfizer License, we have sole responsibility for and control over the development, regulatory approval, manufacture and commercialization of licensed products worldwide, including bearing all costs and expenses associated therewith. We are obligated to use commercially reasonable efforts to develop and seek regulatory approval for one licensed product in the United States and in at least one country out of any of France, Germany, Italy, Japan, Spain or the United Kingdom (Major Market Countries) and, if deemed appropriate by us in our exercise of commercially reasonable efforts, for a second licensed product in the United States or at least one Major Market Country. In addition, we must use commercially reasonable efforts to commercialize a licensed product in the United States and each Major Market Country in which we have received regulatory approval for such product.

Under the Pfizer License, we have paid Pfizer a one-time nonrefundable upfront fee of $5.0 million and a total of $15.0 million in clinical milestones based on first patient dosed in our Phase 3 clinical trials with sulopenem etzadroxil and sulopenem IV and are obligated to pay Pfizer potential future regulatory milestone payments, as well as potential sales milestones upon achievement of net sales ranging from $250.0 million to $1.0 billion for each product type (sulopenem etzadroxil and other prodrugs, and sulopenem and other non-prodrugs). We are obligated to pay Pfizer royalties ranging from a single-digit to mid-teens percentage of marginal net sales of each licensed product. Pfizer also received 381,922 of our Series A preferred shares (which converted to ordinary shares in connection with our initial public offering) at a value of $15.71 per share as additional payment for the licensed rights. In addition, if we sublicense or assign any of our rights to any licensed products to a third party, and we receive in connection with such transaction a threshold amount of at least a low nine figure dollar amount over a specified period of time, we will be obligated to pay Pfizer an additional one-time payment of a low eight figure dollar amount.

At our cost and expense, we are responsible for the prosecution and maintenance of the licensed patents worldwide, using specific legal counsel in various jurisdictions as set forth in the Pfizer License. If we elect to forgo prosecution or maintenance of a licensed patent, we must notify Pfizer and Pfizer has the right to continue prosecution and maintenance of such licensed patent and the exclusive license granted to us under such licensed patent will become a non-exclusive and non-sublicensable license. Subject to certain consultation rights granted to Pfizer, we have the first right, but not the obligation, to enforce the licensed patents at our cost and expense. If we elect to enforce any licensed patent, we may not enter into a settlement agreement that would: (1) adversely affect the validity, enforceability or scope of any of the licensed patents, (2) give rise to any liability for Pfizer, (3) admit non-infringement

of any of the licensed patents or (4) otherwise impair Pfizer's rights in any of the licensed patents or licensed know-how without the prior written consent of Pfizer.

The Pfizer License continues in effect until the expiration of all royalty terms thereunder, unless earlier terminated. Upon such expiration, the Pfizer License shall become non-exclusive, fully-paid, royalty free, perpetual and irrevocable. The royalty term for each licensed product in each country begins as of the first commercial sale of such licensed product in such country and lasts until the later of (1) the expiration of the applicable licensed patents in such country, (2) the expiration of regulatory or data exclusivity for such licensed product in such country and (3) fifteen years after the first commercial sale of such licensed product in such country. Pursuant to the terms of the Pfizer License, each party has the right to terminate the Pfizer License upon the other party's (1) material breach of the Pfizer License that remains uncured after 60 days (or, if the breach cannot be cured in 60 days, up to 150 days) of receipt of notice or (2) insolvency. In addition, we have the unilateral right to terminate the Pfizer License for convenience by providing 90 days' written notice to Pfizer.

**Intellectual Property**

We strive to protect the proprietary technology that we believe is important to our business, including seeking and maintaining rights in 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. However, we do not currently own any patents and rely heavily on the Pfizer License for intellectual property rights that are important or necessary for the development of oral sulopenem and the IV formulation of sulopenem. In addition, we do not license any patent rights that cover the IV formulation of sulopenem and all patent rights covering the compound sulopenem expired prior to us entering into the Pfizer License. We also rely, in some circumstances, 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 in-licensed patents and patents we may own in the future, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how and continuing technological innovation to develop and maintain our proprietary position.

***Licensed Intellectual Property Relating to Oral Sulopenem***

As noted above, we have been granted an exclusive license from Pfizer under one patent in the United States and one patent each in Japan, Mexico and Hong Kong directed to the composition of matter, formulation and/or use of oral sulopenem. Our sulopenem program contains one United States patent covering composition of matter of sulopenem etzadroxil licensed exclusively to us. This United States patent is scheduled to expire in 2029, subject to potential extension under the Hatch-Waxman Act to 2034. The FDA has designated sulopenem and oral sulopenem as QIDPs for the indications of uUTI, cUTI and cIAI as well as community-acquired bacterial pneumonia, acute bacterial prostatitis, gonococcal urethritis, and pelvic inflammatory disease. Fast track designation for these seven indications in both the oral and intravenous formulations has also been granted. QIDP status makes sulopenem eligible to benefit from certain incentives for the development of new antibiotics provided under the GAIN Act. Further, QIDP status could add five years to any other regulatory exclusivity period that may be granted. QIDP status for other indications is also possible given the coverage of gram-negative and gram-positive bacteria by sulopenem, pending submission of additional documentation and acceptance by the FDA. Patent term adjustments or patent term extensions could result in later expiration dates. Fast track status provides an opportunity for more frequent meetings with the FDA, more frequent written communication related to the clinical trials, eligibility for accelerated approval and priority review and the potential for a rolling review.

***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 United States 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 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.

***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 entering into non-disclosure and confidentiality agreements with our employees, consultants, scientific advisors, suppliers, contractors and other third parties. 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 and our trade secrets and other proprietary information may be disclosed. We may not have adequate remedies for any breach and could lose our trade secrets and other proprietary information 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. For more information regarding the risks related to our intellectual property, see the section titled "Risk Factors—Risks Related to our Intellectual Property."

**Competition**

The pharmaceutical 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 obtaining FDA approved drugs and 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 non-competitive or obsolete.

We believe the key competitive factors that will affect the development and commercial success of oral sulopenem and sulopenem, if approved, will be efficacy, coverage of drug-resistant strains of bacteria, safety and tolerability profile, reliability, convenience of oral dosing, price, availability of reimbursement from governmental and other third-party payors and susceptibility to drug resistance.

If approved, oral sulopenem would compete with several oral antibiotics currently in clinical development, including ceftibuten clavulanate from Achaogen, Inc., tebipenem pivoxil from Spero Therapeutics, Inc., delafloxacin from Melinta Therapeutics, Inc, pivmecillinam from Utility Therapeutics Limited, ETX0282CPDP (a novel ß-lactamase inhibitor combined with cefpodoxime proxetil) from Entasis Therapeutics Holdings Inc. and omadacycline from Paratek Pharmaceuticals, Inc.

We also expect that oral sulopenem, if approved, would compete with future and current generic versions of marketed oral antibiotics such as levofloxacin, ciprofloxacin, nitrofurantoin, fosfomycin, amoxicillin-clavulanate, cephalexin and trimethoprim-sulfamethoxazole. If approved, we believe that oral sulopenem would compete effectively against these compounds on the basis of sulopenem's potential:

- broad range of activity against a wide variety of resistant and MDR gram-negative bacteria;
- low probability of drug resistance;
- favorable safety and tolerability profile;
- convenient oral dosing regimen and opportunity to step down from IV-administered therapy; and
- use as a monotherapy treatment for resistant and MDR gram-negative infections.

If approved, sulopenem would compete with several IV-administered product candidates marketed for the treatment of gram-negative infections, including Avycaz from Allergan plc and Pfizer, Zerbaxa from Merck & Co., Vabomere from Melinta Therapeutics, Inc., Zemdri from Achaogen, Inc, and Xerava from Tetraphase Pharmaceuticals, Inc. There are also a number of IV-administered product candidates in late-stage clinical development that are intended to treat gram-negative infections, including cefiderocol from Shionogi & Co. Ltd., Contepo from Nabriva Therapeutics plc (as successor to Zavante Therapeutics, Inc.) and imipenem-relabactam from Merck & Co.

If approved, we believe that sulopenem would compete effectively and potentially occupy an earlier place in treatment against these compounds on the basis of sulopenem's potential, including that sulopenem:

- allows physicians to stay in the same molecule with stepdown therapy to oral sulopenem;
- has a convenient once a day dosing over a three-hour infusion period;

- has a broad spectrum activity against a wide variety of resistant and MDR gram-negative bacteria;
- has a low probability of drug resistance; and
- has a favorable safety and tolerability profile.

**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, recordkeeping, labeling, advertising, promotion, distribution, marketing, sales, 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 other countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

***United States Government Regulation***

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act (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. The 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 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 good laboratory practices (GLP) regulations;
- submission to the FDA of an investigational new drug (IND) application which must become effective before human clinical trials may begin;
- approval by an independent institutional review board (IRB) at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices (GCPs) to establish the safety and efficacy of the proposed drug product for each indication;
- submission to the FDA of an NDA;
- satisfactory completion of an FDA advisory committee review, if applicable;
- 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 (cGMP), and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of clinical data;
- payment of user fees and securing FDA review and approval of the NDA; and
- commitment to comply with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy (REMS), and the potential requirement to conduct post-approval studies.

*Preclinical Studies*

Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. Preclinical tests intended for submission to the FDA to support the safety of a product candidate must be conducted in compliance with GLP regulations and the United States Department of Agriculture's Animal Welfare Act. A drug sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such

a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. Clinical holds are imposed by the FDA whenever there is concern for patient safety and may be a result of new data, findings, or developments in clinical trials, nonclinical studies, and/or CMC. 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. 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.

*Clinical Trials*

Clinical trials involve the administration of the investigational product 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 at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution. Information about, and results from, certain clinical trials must be submitted within specific timeframes to the National Institutes of Health 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 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 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.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Results from one trial may not be predictive of results from subsequent trials. 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 if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

*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.

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.

*Marketing Approval*

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, 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 federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2019 is $2,588,478 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2019 is $309,915. Under the Prescription Drug User Fee Act (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 the FDA because the FDA has approximately two months to make a "filing" decision. 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.

The FDA also may require submission of a REMS plan 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 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 facilities in which it is manufactured, processed, packaged or held meet standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is 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 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 GCPs and the FDA is able to validate the data through an on-site inspection, if deemed necessary. 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, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met before the NDA and 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. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

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, 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 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 GAIN Act. We obtained a QIDP designation for sulopenem and oral sulopenem for the indications of cUTI, uUTI and cIAI in 2016 and 2017, respectively, and the indications of community-acquired bacterial pneumonia, acute bacterial prostatitis, gonococcal urethritis, and pelvic inflammatory disease in 2019 and fast track designation for these seven indications in both the oral and intravenous formulations has also been granted. 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 based on efficacy or safety factors. 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, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA. The FDA may decide to rescind the fast track designation if it determines that the qualifying criteria no longer apply.

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. These six and ten month review periods are measured from the "filing" date for NDAs for new molecular entities. The FDA will automatically give a priority review designation for the first application submitted in respect of a product for which a QIDP designation was granted, such as sulopenem and oral sulopenem.

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.

*Post-Approval Requirements*

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 recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product label, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are

continuing, annual program user fee requirements for any marketed products, 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 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;
- fines, 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 or criminal penalties.

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

*Exclusivity and Approval of Competing Products*

*Hatch-Waxman Exclusivity*

Market and data exclusivity provisions under the FDCA can delay the submission or the approval of certain applications for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the activity of the drug substance. We believe that our product candidates are new chemical entities. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application (ANDA), or a 505(b)(2) NDA, submitted by another company that references the previously approved drug. However, an ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of marketing exclusivity for an NDA, 505(b)(2) NDA, or

supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant, are deemed by the FDA to be essential to the approval of the application or supplement. Three-year exclusivity may be awarded for changes to a previously approved drug product, such as new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

*Qualified Infectious Disease Product Exclusivity*

Under the GAIN Act, the FDA may designate a product as a QIDP. In order to receive this designation, a drug must qualify as an antibiotic or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by either (i) an antibiotic or antifungal resistant pathogen, including novel or emerging infectious pathogens, or (ii) a so-called "qualifying pathogen" found on a list of potentially dangerous, drug-resistant organisms established and maintained by the FDA. A sponsor must request such designation before submitting a marketing application. We obtained QIDP designation for sulopenem and oral sulopenem for the indications of cUTI, uUTI and cIAI in 2016 and 2017, respectively, as well as for the indications of community-acquired bacterial pneumonia, acute bacterial prostatitis, gonococcal urethritis, and pelvic inflammatory disease in 2019. Fast track designation for these seven indications in both the oral and intravenous formulations has also been granted.

Upon approving an application for a QIDP, the FDA will extend by an additional five years any regulatory 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 Act 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 QIDP based on the uses for which it is ultimately approved.

*Pediatric Exclusivity*

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 or biologics license application sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data does 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.

***Regulation Outside of the United States***

In addition to regulations in the United States, we will be subject to a variety of regulations governing clinical trials and commercial sales and distribution of our products outside of the United States. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of other countries or economic areas, such as the European Union, 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 European Union regulatory systems, a company may submit marketing authorization applications either under a centralized or decentralized procedure. 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 medicines, and optional for other medicines which are highly innovative. Under the centralized procedure, a marketing application is submitted to the 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 within 67 days of receipt of the opinion. The initial marketing authorization is valid for five years, but once renewed is usually valid for an unlimited period. The decentralized procedure provides for approval by one or more "concerned" member states based on an assessment of an application performed by one member state, known as the "reference" member state. Under the decentralized approval procedure, an applicant submits an application, or dossier, and related materials to the reference member state and concerned member states. The reference member state

prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report, each concerned member state must decide whether to approve the assessment report and related materials. If a member state does not recognize the marketing authorization, the disputed points are eventually referred to the European Commission, whose decision is binding on all member states.

*Brexit and the Regulatory Framework in the United Kingdom*

On June 23, 2016, the electorate in the United Kingdom (UK) voted in favor of leaving the European Union (EU) (commonly referred to as "Brexit"). Thereafter, on March 29, 2017, the country formally notified the EU of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the UK from the EU will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the UK provides a notice of withdrawal pursuant to the EU Treaty, unless extended. Since the regulatory framework for pharmaceutical products in the UK covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the UK. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the UK .

The UK has a period of two years from the date of its formal notification to negotiate the terms of its withdrawal from, and future relationship with, the EU, unless extended. If no formal withdrawal agreement is reached between the UK and the EU, then it is expected the UK's membership of the EU will automatically terminate on April 12, 2019. Discussions between the UK and the EU focused on finalizing withdrawal issues and transition agreements are ongoing. However, limited progress to date in these negotiations and ongoing uncertainty within the UK government and Parliament sustains the possibility of the UK leaving the EU on April 12, 2019 without a withdrawal agreement and associated transition period in place, which is likely to cause significant market and economic disruption.

*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 European Union, 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 Coverage and Reimbursement**

Sales of drug products 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. Obtaining coverage and reimbursement approval for a drug product from third-party payors is a time-consuming and costly process that can require the provision of supporting scientific, clinical and cost effectiveness data for the use of drug products to the payor. There may be significant delays in obtaining such coverage and reimbursement for newly approved drug products, and coverage may be more limited than the purposes for which the drug product is approved by the FDA or similar regulatory authorities outside of the United States. Moreover, eligibility for coverage and reimbursement does not imply that a drug product will be paid for in all cases or at a rate that covers operating costs, including research, development, intellectual property, manufacture, sale and distribution expenses. Reimbursement rates may vary according to the use of the drug product and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drug products and may be incorporated into existing payments for other services.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved drug products. In the United States, third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies, but also have their own methods and approval process apart from Medicare coverage and reimbursement determinations. It is difficult to predict what third-party payors will decide with respect to coverage and reimbursement for new drug products. An inability to promptly obtain coverage and adequate reimbursement rates from third-party payors for any approved drug

products could have a material adverse effect on a pharmaceutical manufacturer's operating results, ability to raise capital needed to commercialize drug products and overall financial condition.

Reimbursement may impact the demand for, and/or the price of, any drug product which obtains marketing approval. Even if coverage is obtained for a given drug product by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third-party payors to reimburse all or part of the costs associated with those medications. Patients are unlikely to use a drug product, and physicians may be less likely to prescribe a drug product, unless coverage is provided and reimbursement is adequate to cover all or a significant portion of the cost of the drug product. Therefore, coverage and adequate reimbursement is critical to new drug product acceptance. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available.

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 U.S. 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 drug 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 a pharmaceutical manufacturer's net revenue and results.

In addition, it is expected that the increased emphasis on managed care and cost containment measures in the United States by third-party payors will continue and place further pressure on pharmaceutical pricing and coverage. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more drug products that gain regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

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 (the Price Transparency Directive). The aim of the Price Transparency 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 (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, such as the National Institute for Health and Care Excellence in the United Kingdom, 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 the United Kingdom, when adopting decisions concerning the pricing and reimbursement of a specific medicinal product.

**Other Healthcare Laws**

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of drug product candidates which obtain marketing approval. In addition to FDA restrictions on marketing of pharmaceutical products, pharmaceutical manufacturers are exposed, directly, or indirectly, through customers, to broadly applicable fraud and abuse and other

healthcare laws and regulations that may affect the business or financial arrangements and relationships through which a pharmaceutical manufacturer can market, sell and distribute drug products. Such laws include, without limitation:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, in return for either the referral of an individual, or the purchase, leasing, furnishing or arranging for the purchase, lease or order of a good, facility, item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers and formulary managers on the other hand. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, (ACA) amended the intent requirement of the federal Anti-Kickback Statute, such that a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it;
- the federal false claims and civil monetary penalty laws, including the federal False Claims Act, which prohibits, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid or other government payors that are false or fraudulent. In addition, the ACA provides, and recent government cases against pharmaceutical and medical device manufacturers support the view, that federal Anti-Kickback Statute violations and certain marketing practices, including off-label promotion, may implicate the federal False Claims Act. Further, pharmaceutical manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. Criminal prosecution is 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 (HIPAA), which, among other things, imposes criminal liability for executing or attempting to execute a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and creates federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statements or representations, 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, benefits, items or services;
- HIPAA, as amended by the Health Information Technology and Clinical Health Act of 2009 (HITECH) and its implementing regulations, which impose certain requirements relating to the privacy, security, transmission and breach reporting of individually identifiable health information upon certain health plans, healthcare clearinghouses and healthcare providers and their respective business associates that perform services for them that involve individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in U.S. federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions;
- the federal physician payment transparency requirements, sometimes referred to as the "Physician Payments Sunshine Act," and its implementing regulations, which require 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 (HHS) information related to payments or other transfers of value made 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;
- state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws, that may impose similar or more prohibitive restrictions, and may apply to items or services reimbursed by non-governmental third-party payors, including private insurers; and
- state and foreign laws that require pharmaceutical companies to implement compliance programs, comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or to track and report gifts, compensation and other remuneration provided to physicians and other healthcare providers, state and local laws that require the registration of pharmaceutical sales representatives, and other federal, state and foreign laws that govern the privacy and security of health information or personally identifiable information in certain circumstances, including state health information privacy and data breach notification laws which govern the collection, use, disclosure, and protection of health-related and other personal information, many of which differ from each other in significant ways and often are not pre-empted by HIPAA, thus requiring additional compliance efforts.

Because of the breadth of these laws and the narrowness of their exceptions and safe harbors, it is possible that business activities can be subject to challenge under one or more of such laws. The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry.

Ensuring that business arrangements with third parties comply with applicable healthcare laws and regulations is costly and time consuming. If business operations are found to be in violation of any of the laws described above or any other applicable governmental regulations a pharmaceutical manufacturer may be subject to penalties, including civil, criminal and administrative penalties, damages, fines, disgorgement, individual imprisonment, exclusion from governmental funded healthcare programs, such as Medicare and Medicaid, contractual damages, reputational harm, diminished profits and future earnings, additional reporting obligations and oversight if subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, and curtailment or restructuring of operations, any of which could adversely affect a pharmaceutical manufacturer's ability to operate its business and the results of its operations.

**Healthcare Reform**

In the United States, there have been, and continue to be, a number of legislative and regulatory changes and proposed changes to the healthcare system that could affect the future results of pharmaceutical manufacturers' operations. In particular, there have been and continue to be a number of initiatives at the federal and state levels that seek to reduce healthcare costs. Most recently, ACA, which was enacted in March 2010, includes measures to significantly change the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA, of greatest importance to the pharmaceutical and biotechnology industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively, and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price (AMP);
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics that are inhaled, infused, instilled, implanted or injected;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (and 70% commencing on January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- expansion of the entities eligible for discounts under the Public Health program;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- establishment of a Center for Medicare Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending; and
- implementation of the federal physician payment transparency requirements, sometimes referred to as the "Physician Payments Sunshine Act."

Some of the provisions of the ACA have yet to be implemented, and there have been legal and political challenges to certain aspects of the ACA. Since January 2017, President Trump has signed two executive orders and other directives designed to delay, circumvent, or loosen certain requirements mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the 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 that is commonly referred to as the "individual

mandate." Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, 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 (the BBA), among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". Congress may consider other legislation to repeal or replace elements of the ACA. More recently, in July 2018, CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. We continue to evaluate how the ACA and recent efforts to repeal and replace or limit the implementation of the ACA will impact our business.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Further, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, 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. Under this blueprint for action, the Trump administration indicated that HHS will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases.

HHS has already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. Although a number of these, and other potential proposals, 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. For example, on January 31, 2019, the HHS Office of Inspector General proposed modifications to the federal Anti-Kickback Statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations.

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.

**Commercialization Strategy and Organization**

Given our stage of development, we have not yet established a commercial organization or distribution capabilities. If approved, we intend to commercialize our sulopenem program in the United States with a commercial partner and/or on our own with a targeted sales force across the community and hospital settings.

Prior to receiving approval, we plan to establish a health resources group to familiarize doctors in the community setting with the rising rate of resistance of pathogens to the current oral therapies for UTI. If approved, we will direct our health resources group to promote antibiotic stewardship, particularly of oral sulopenem, by educating physicians in the community setting about patients for whom sulopenem may be an appropriate treatment option. In the hospital setting, we believe our sulopenem program will support stewardship efforts in the hospital focused on reduction in treatment length-of-stay by providing a safe and effective oral therapy that can be completed in an outpatient setting. Our health resources group will also work with hospitals, provider organizations and payors to demonstrate that the use of sulopenem may reduce the length of a patients' hospital stay or avoid hospital admission altogether, which we believe would lower the total cost of treatment of cUTI, and in some cases uUTI when inappropriate therapy leads to higher hospitalization rates or poor clinical outcomes for elevated risk patients. In addition, we expect that our health resources group will also work with doctors in the infectious disease field to answer questions regarding sulopenem's clinical results and its pharmacokinetic profile, conduct medical education events regarding the emerging science and build awareness of sulopenem.

If the FDA approves oral sulopenem and sulopenem, we plan to build a commercial infrastructure to launch both product candidates in the United States. We expect that our commercial infrastructure, led by highly-experienced management personnel, would be comprised of a targeted sales force, an internal marketing and health resources group, as well as a managed markets group focused on reimbursement activities with third-party payors and a specialty distribution team. We also plan to have in place a patient and healthcare practitioner support group to assist with information requests, reimbursement logistics and assistance, and provide educational materials where appropriate. To ensure successful execution of these critical activities, we may need to hire personnel to fill some of these functions in advance of the anticipated approval date. Further, if we choose to engage with a commercial partner in the United States, we would expect to reach a broader percentage of the market for sulopenem.

We expect to direct our sales and marketing efforts toward the community and hospital practitioner settings that account for a substantial majority of the potential market for oral sulopenem and sulopenem across geographies with the highest prevalence of bacterial resistance to fluoroquinolones. Based on a 2017 market survey data of outpatient urine cultures of Enterobacteriaceae and quinolone resistance by zip code, we estimate that our initial sales force could successfully target key customers including top hospitals and emergency room clinics, as well as specialty and primary care practices in the community setting. As access for, and awareness of, our sulopenem program increases, we would plan to broaden our target audience and geography by increasing the number of sales representatives to capture a larger percentage of the market.

We are focusing our initial commercial efforts on the U.S. market, which we believe represents the largest market opportunity for our sulopenem program. We are currently evaluating our commercialization strategy outside the United States, and believe that Europe and Asia represent significant opportunities because of rising rates of ESBL and quinolone resistance in these geographies, which in many countries exceeds the United States' resistance rate.

**Manufacturing**

We do not currently own or operate manufacturing facilities for the production of any of our product candidates. We currently rely on four third-party contract manufacturers for all of our required raw materials, drug substance, and finished drug product for our preclinical research and clinical trials. We currently have an 11-person team dedicated to managing the relationships with these manufacturers and the manufacturing process. Due to the complex and critical nature of drug manufacturing, we have employed a dual sourcing strategy in order to register two suppliers and validate at least one supplier for sulopenem's API at the time of submitting our NDAs, with each supplier capable of producing commercial scale quantities under cGMP conditions. We also intend to have a third-party manufacturer to produce the oral sulopenem bilayer tablets. In the future, given the importance of our oral formulation, we plan to pursue additional sources to manufacture tablets. We plan to use another third party to manufacture the IV vials. Potential additional sources to manufacture IV vials have also been identified.

**Employees**

As of December 31, 2018, we had 48 full-time employees, including a total of nine employees with M.D., Pharm.D. or Ph.D. degrees. 37 employees were primarily engaged in research and development activities, with the rest providing administrative, business and operations support. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our employee relations to be good.

**Our Corporate Information**

We were incorporated under the laws of the Republic of Ireland in June 2015 as a limited company and re-registered as a public limited company on March 20, 2018. Our principal executive offices are located at Block 2 Floor 3, Harcourt Centre, Harcourt Street, Dublin 2, Ireland, and our telephone number is (+353) 1 903-8920.

**Available Information**

We maintain a website with the address www.iterumtx.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 Securities Exchange Act of 1934 (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. You can review our electronically filed reports, proxy and information statements and other information that we file with the SEC on the SEC's web site at http://www.sec.gov. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Annual Report on Form 10-K.

**Item 1A. Risk Factors.**

*Careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10-K and in other documents that we file with the SEC, in evaluating our company and our business. Investing in our ordinary shares involves a high degree of risk. If any of the events described in the following Risk Factors and the risks described elsewhere in this Annual Report on Form 10-K actually occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected. In these circumstances, the market price of our ordinary shares could decline, and you may lose all or part of your investment.*

**Risks Related to Our Financial Position and Capital Requirements**

***We have incurred net losses in each year since our inception and anticipate that we will continue to incur significant losses unless we successfully commercialize our sulopenem program.***

We are a clinical-stage pharmaceutical company with a limited operating history. We have not generated any product revenue and have incurred net losses in each year since our inception in 2015. As of December 31, 2018, we had an accumulated deficit of $131.8 million. Our product candidates, oral sulopenem and sulopenem (together, the sulopenem program), are in clinical development, and have not been approved for sale and we may never have our product candidates approved for commercialization. We have financed our operations to date primarily through private placements of our preferred shares and, more recently, through our initial public offering of ordinary shares (IPO) in May 2018 and a private placement of our ordinary shares in December 2018, being the subscription for 190,615 ordinary shares by our supplier as described in Note 8 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K. In April 2018, we entered into a secured credit facility with Silicon Valley Bank (SVB) and made an initial drawdown of $15.0 million. We have devoted substantially all of our financial resources and efforts to research and development, including preclinical and clinical development, for our sulopenem program.

We expect to continue to incur significant expenses and increasing operating losses as we conduct our ongoing and planned clinical trials of oral sulopenem and sulopenem, seek marketing approval for such product candidates if clinical trials are successful, and pursue the development of our sulopenem program in additional indications through preclinical and clinical development. Our expenses will also increase substantially if and as we:

- conduct additional clinical trials for oral sulopenem and sulopenem, which include our three ongoing Phase 3 clinical trials, and our ongoing and planned Phase 1 clinical trials, which we expect to occur through 2019;
- initiate other studies as part of our sulopenem program, some of which may be required for regulatory approval of our product candidates;
- establish a sales, marketing and distribution infrastructure to commercialize oral sulopenem and sulopenem in the United States if we obtain marketing approval from the U.S. Food and Drug Administration (FDA) and we choose to commercialize directly in the United States;
- establish manufacturing and supply chain capacity sufficient to provide commercial quantities of oral sulopenem and sulopenem, if we obtain marketing approval;
- pursue the development of our sulopenem program in additional indications;
- maintain, expand, defend and protect our intellectual property portfolio;
- hire additional clinical, scientific and commercial personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts, as well as to support our ongoing transition to a public reporting company; and
- acquire or in-license other product candidates or technologies.

***We are substantially dependent on the success of our two product candidates, oral sulopenem and sulopenem, and if we are unable to achieve and sustain profitability, the market value of our ordinary shares will likely decline.***

Our ability to become and remain profitable depends on our ability to generate revenue. To date, we have invested substantially all of our efforts and financial resources in the development of oral sulopenem and sulopenem, which are currently our two product candidates in development. Our prospects, including our ability to finance our operations and generate revenue from product sales, will currently depend entirely on the development and commercialization of our sulopenem program.

We do not expect to generate significant revenue unless and until we obtain marketing approval for, and commercialize, oral sulopenem and sulopenem. Our ability to generate future revenue from product sales will require us to be successful in a range of challenging clinical and commercial activities, including:

- enrolling and successfully completing the ongoing Phase 3 clinical trials in our three initial indications;
- applying for and obtaining marketing approval for oral sulopenem and sulopenem;
- protecting and maintaining our rights to our intellectual property portfolio related to our sulopenem program;
- establishing and maintaining supply and manufacturing relationships with third parties that can support clinical development and can provide adequate commercial quantities of oral sulopenem and sulopenem, if approved;
- establishing sales, marketing and distribution capabilities to effectively market and sell oral sulopenem and sulopenem, or entering into collaboration arrangements for the commercialization of oral sulopenem and sulopenem where we choose not to commercialize directly ourselves; and
- obtaining market acceptance of oral sulopenem and sulopenem as viable treatment options.

Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when, or if, we will become profitable. We may never succeed in any or all of these activities and, even if we do, we may never generate revenue that is significant or large enough to achieve profitability. Our expenses could increase if we are required by the FDA, the European Medicines Agency (EMA), or any comparable foreign regulatory authority, to perform different studies or studies in addition to those currently expected, or if there are any delays in completing our clinical trials, including delays or expense associated with increasing the sample size of any study, or with the development of our sulopenem program or any future product candidates. Even if oral sulopenem or sulopenem are approved for commercial sale, we anticipate incurring significant costs associated with the commercial launch of oral sulopenem and sulopenem. Where we enter into collaboration arrangements with third-party collaborators for commercialization of product candidates, our product revenues or the profitability of these product revenues to us would likely be lower than if we were to directly market and sell products in those markets.

Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company could cause our shareholders to lose all or part of their investment.

***We will require additional capital to fund our operations, and if we fail to obtain financing when needed or on acceptable terms, we may not be able to complete the development and commercialization of our sulopenem program.***

Developing pharmaceutical products is a time-consuming, expensive and uncertain process that takes years to complete. We expect that our expenses will increase substantially as we advance our clinical trials of oral sulopenem and sulopenem, seek marketing approval for such product candidates if clinical trials are successful, and pursue the development of our sulopenem program in additional indications through preclinical and clinical development. If we obtain marketing approval for oral sulopenem, sulopenem or any future product candidate, we expect to incur significant commercialization expenses related to product sales, marketing, distribution and manufacturing. Some of these expenses may be incurred in advance of marketing approval, and could be substantial.

Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources. 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 effect on our financial condition and our ability to develop and commercialize our sulopenem program and otherwise pursue our business strategy.

We believe that our existing cash, cash equivalents, short-term investments, and available borrowings under our credit facility, will enable us to fund our operating expenses and capital expenditure requirements through the first quarter of 2020. We have based these estimates on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect. We expect that we will require additional capital to file with regulatory agencies and commercialize oral sulopenem and sulopenem, if we receive regulatory approval. If we receive regulatory approval for oral sulopenem or sulopenem, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution.

Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical product candidates, we are unable to estimate the exact amount of our working capital requirements. Changing circumstances could cause us to consume capital significantly faster than we currently anticipate, and we may need to spend more than currently expected because of circumstances beyond our control. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the timing and costs of our ongoing clinical trials of oral sulopenem and sulopenem, including our three Phase 3 clinical trials in our three initial indications;
- the initiation, progress, timing, costs and results of preclinical studies and clinical trials of other potential product candidates and of our current product candidates in additional indications;
- the amount of funding that we receive under government awards that we have applied for or may apply for in the future;
- the number and characteristics of product candidates that we pursue;
- the outcome, timing and costs of seeking regulatory approvals;
- the costs of commercialization activities for oral sulopenem and sulopenem and other product candidates if we receive marketing approval, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- the receipt of marketing approval and revenue received from any potential commercial sales of oral sulopenem and sulopenem;
- the terms and timing of any future collaborations, licensing 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 pursuant to an exclusive license agreement with Pfizer Inc. (Pfizer) (the Pfizer License) or other future license agreements;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against any intellectual property related claims;
- the costs of operating as a public company; and
- the extent to which we in-license or acquire other products and technologies.

***Our indebtedness imposes certain operating and other restrictions on us and could adversely affect our ability to raise additional capital.***

On April 27, 2018, our subsidiaries, Iterum Therapeutics International Limited, Iterum Therapeutics US Holding Limited and Iterum Therapeutics US Limited (Borrowers), entered into a loan and security agreement with SVB pursuant to which SVB agreed to lend the Borrowers up to $30.0 million in two term loans. $15.0 million of the secured credit facility was funded on closing and the other $15.0 million is available at our option upon the satisfaction of certain draw requirements (as described in Note 12 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K). Obligations under the secured credit facility are secured by substantially all of our existing and future assets and the existing and future assets of our subsidiaries, including intellectual property. Our secured credit facility imposes operating and other restrictions on us. Such restrictions affect, and in many respects limit or prohibit, our ability to, among other things, dispose of certain assets, pay dividends and incur additional indebtedness. Failure to make payments or comply with these and other terms and covenants under our secured credit facility could result in an event of default, which could lead to an acceleration of amounts due and foreclosure upon and/or sale or other liquidation of all of our and our subsidiaries' assets, including intellectual property. Any of the foregoing would have a material adverse effect on our operations and financial condition. In addition, this indebtedness and the security interests granted to secure it could make it more difficult for us to raise additional capital to fund our operations.

***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 November 2015. Since our inception, we have devoted substantially all of our financial resources and efforts to organizing and staffing our company, business planning, raising capital, planning for potential commercialization, and research and development, including preclinical and clinical development, for our sulopenem program. While the members of our development team have successfully developed and registered other antibiotics in past roles at different companies, our company has limited experience and has not yet demonstrated an ability to successfully complete a large-scale, pivotal clinical trial, obtain marketing approval, manufacture a commercial scale product (or arrange for a third party to do so on our behalf), or 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.

Assuming we obtain marketing approval for oral sulopenem and sulopenem, we will need to transition from a company with a research and development focus to a company capable of supporting commercial activities whether we choose to commercialize product candidates directly ourselves or seek to commercialize them through third-party collaboration arrangements. We may encounter unforeseen expenses, difficulties, complications and delays, and may not be successful in such a transition.

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

Unless and until we can generate a substantial amount of revenue from our sulopenem program or future product candidates, we expect to finance our future cash needs through equity offerings, debt financings, collaboration agreements, other third-party funding, strategic alliances, licensing arrangements, marketing and distribution arrangements or government funding. 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.

Our issuance of additional securities, whether equity or debt, or the possibility of such issuance, may cause the market price of our ordinary shares to decline, and our shareholders may not agree with our financing plans or the terms of such financings. To the extent that we raise additional capital through the sale of ordinary shares, convertible securities or other equity securities, the ownership interests of our then existing shareholders may be materially diluted, and the terms of these securities could include liquidation or other preferences and antidilution protections that could adversely affect the rights of our then existing shareholders. In addition, if we make an additional draw under our secured credit facility, we will be required to issue additional warrants. Further 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, which could adversely affect 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 of our 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 or product candidates or grant licenses on terms that may not be favorable to us.

***We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.***

Because we have limited financial resources, we intend to focus on developing our sulopenem program for the specific indications of uncomplicated urinary tract infections (uUTI), complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI), all of which are focused on what we believe to be the most pressing near-term medical needs, in terms of both their potential for marketing approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other potential product candidates or developing our sulopenem program in other indications that may prove to have greater commercial potential.

Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to the product candidate.

**Risks Related to Clinical Development and Commercialization**

***We are heavily dependent on the success of our sulopenem program, and our ability to develop, obtain marketing approval for and successfully commercialize oral sulopenem and sulopenem. If we are unable to obtain marketing approvals for oral sulopenem or sulopenem, or if thereafter we fail to commercialize oral sulopenem or sulopenem or experience significant delays in doing so, our business will be materially harmed.***

We currently have no products approved for sale and have invested substantially all of our efforts and financial resources in the development of our sulopenem program as the first and only oral and intravenous (IV) branded penem available globally. Our near-term prospects are substantially dependent on our ability to develop, obtain marketing approval for and successfully commercialize oral sulopenem and sulopenem. The success of our sulopenem program will depend on several factors, including the following:

- successful enrollment in, and completion of, clinical trials, including our three ongoing pivotal Phase 3 clinical trials of oral sulopenem and sulopenem;
- clinical trial results with safety, tolerability and efficacy profiles that are satisfactory to the FDA or any comparable foreign regulatory authority;
- timely completion of any additional clinical trials and non-clinical studies conducted to support the filing for regulatory approvals of our sulopenem program, if required by the FDA or any comparable foreign regulatory authority;
- receipt of marketing approvals from applicable regulatory authorities;
- establishment and maintenance of arrangements with third-party manufacturers to obtain commercial supply at a scale sufficient to meet anticipated demand and at a cost appropriate for our commercialization;
- acquisition and maintenance of patent, trade secret and other intellectual property protection and regulatory exclusivity, both in the United States and internationally, including our ability to maintain our license agreement with Pfizer;
- protection of our rights in our intellectual property portfolio;
- launch of commercial sales of oral sulopenem and sulopenem, if approved, whether alone or in collaboration with others;
- the effectiveness of our own or any future collaborators' marketing, sales and distribution strategy and operations;
- acceptance of oral sulopenem and sulopenem, if approved, by patients, physicians and the medical community at large;
- our ability to obtain and sustain coverage and an adequate level of reimbursement by third-party payors;
- the prevalence, frequency and severity of adverse side effects of oral sulopenem and sulopenem;
- the availability, perceived advantages, relative cost and relative efficacy of alternative and competing therapies; and
- an acceptable safety profile of oral sulopenem and sulopenem following approval.

Many of these factors are beyond our control, including clinical development, the regulatory submission process, potential threats to our intellectual property rights, manufacturing and the impact of competition. If we are unable to develop, receive marketing approval for, or successfully commercialize oral sulopenem and sulopenem, or if we experience delays as a result of any of these factors or otherwise, our business could be materially harmed.

***Our company has no experience in obtaining regulatory approval for a drug.***

Our company has never obtained regulatory approval for, or commercialized, a drug. We must complete extensive preclinical and clinical trials to demonstrate the safety and efficacy of our product candidates in humans before we will be able to obtain these approvals. To gain approval to market a product candidate, we must provide the FDA and foreign regulatory authorities with non-clinical, clinical and chemistry, manufacturing, and controls (CMC) data that adequately demonstrates the safety and efficacy of the product for the intended indication(s) applied for in the new drug application (NDA) or other respective regulatory filing. It is possible that the FDA may refuse to accept any or all of our planned NDAs for substantive review or may conclude after review of our data that our application is insufficient to obtain regulatory approval for any current or future product candidates. If the FDA does not approve any of our planned NDAs, it may require that we conduct additional costly clinical, non-clinical or manufacturing validation studies before it will reconsider our applications. Depending on the extent of these or any other FDA-required studies, approval of any NDA or other application that we submit may be significantly delayed, possibly for several years, or may require us to expend more resources than we have available.

Any failure or delay in obtaining regulatory approvals would prevent us from commercializing oral sulopenem and sulopenem, generating revenues and achieving and sustaining profitability. It is also possible that additional studies, if performed and completed, may not be considered sufficient by the FDA to approve any NDA or other application that we submit. If any of these outcomes occur,

we may be forced to abandon the development of our product candidates, which would materially adversely affect our business and could potentially cause us to cease operations. We face similar risks for our applications in other countries.

***If clinical trials of oral sulopenem, sulopenem or any other product candidate that we may 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 oral sulopenem, sulopenem or any other product candidate.***

We may not 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. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. We have not previously submitted an NDA to the FDA or similar applications to comparable foreign regulatory authorities for any of our product candidates.

Our business currently depends entirely on the successful development, regulatory approval and commercialization of our sulopenem program. The clinical development of our sulopenem program, or any future product candidates, is susceptible to the risk of failure inherent at any stage of drug development, including failure to demonstrate efficacy in a clinical 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. A number of companies in the pharmaceutical industry, including biotechnology companies, have suffered significant setbacks in clinical trials, even after promising results in earlier non-clinical studies or clinical trials. The results of preclinical and other non-clinical studies and/or early clinical trials of our product candidates or future product candidates may not be predictive of the results of later-stage clinical trials and interim results of a clinical trial do not necessarily predict final results. Notwithstanding any promising results in early non-clinical studies or clinical trials, we cannot be certain that we will not face similar setbacks.

For example, we present data from clinical trials conducted by Pfizer Japan in the 1990s. The data from those clinical trials is not directly comparable to data from clinical trials that would be conducted today or the data that we anticipate from our Phase 3 program for a variety of reasons, including that protocols were designed for different purposes and as a consequence had different enrollment and efficacy evaluation criteria. For example, while a subjective investigator assessment of outcome is typically included in all cUTI protocols and was performed in the Japanese program, more structured endpoints are required as part of current FDA guidelines for registrational trials. Current FDA guidelines define the primary efficacy outcome based on both clinical and microbiological success, while EMA guidelines recommend microbiologic outcome. The structured endpoint in the Japanese program assessed outcome based on resolution of pyuria and microbiologic outcome. In addition, the pathogens isolated in the course of a clinical trial will vary depending on the types of patients enrolled, the geographic location of the sites that contribute to the study and the year in which the study is performed. While the organisms seen in the Japanese study are similar to those we anticipate in the Phase 3 program, we expect the frequency distribution of these pathogens may be different. Furthermore, adverse event reports can vary by geographic region and we may see a different adverse event rate and different types of events in patients that we study in the Phase 3 program relative to the experience in Japan.

In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Although data from Phase 1 and Phase 2 clinical trials of oral sulopenem and sulopenem provides support for the overall safety profile of the product candidates, 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 clinical 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, among others. It is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one of the factors listed or otherwise. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials, we may fail to detect toxicity of or intolerability of our product candidates or may determine that our product candidates are toxic or not well tolerated when that is not in fact the case. 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 assure our shareholders that any ongoing clinical trials that we are conducting or 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 encounter unforeseen events prior to, during, or as a result of, clinical trials that could delay or prevent us from obtaining regulatory approval for oral sulopenem, sulopenem or any of our other product candidates, including:

- although we are conducting our Phase 3 clinical trials pursuant to Special Protocol Assessment (SPA) agreements, the FDA or other comparable foreign regulatory authorities may ultimately disagree as to the design or implementation of our Phase 3 clinical trials or other clinical trials;
- we may not reach agreement on acceptable terms with all clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different trial sites;
- 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;
- 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;
- the FDA, the local National Health Authorities 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 a product candidate for various reasons, including non-compliance 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;
- 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; or
- 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.

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

- incur additional unplanned costs;
- 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
- be required to remove the product from the market after obtaining marketing approval.

Our failure to successfully initiate and complete clinical trials of our product candidates and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any of our product candidates would significantly harm our business. We cannot assure our shareholders that our three ongoing Phase 3 clinical trials will be completed on schedule, if at all, or that we will not need to restructure our clinical trials. 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, delays of clinical trials may ultimately lead to the denial of regulatory approval of oral sulopenem, sulopenem or any other product candidate.

***If we experience delays or difficulties in the enrollment of patients in clinical trials, clinical development activities could be delayed or otherwise adversely affected.***

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion. We may not be able to continue or complete our ongoing

Phase 3 clinical trials or initiate, continue or complete other clinical trials of oral sulopenem, sulopenem or any other product candidate thatwe develop if we are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials 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 participation in the clinical trial;
- the number of sites at which we conduct the trial and the speed at which we are able to open such sites;
- the prevalence of antibiotic resistance to pathogens where we conduct the clinical trial;
- the accuracy of certain estimates and assumptions upon which the design of the protocols are predicated;
- our ability to recruit clinical trial investigators with appropriate experience;
- competing clinical trials and clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications that we are investigating;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will drop out of the clinical trials before completion.

The inclusion and exclusion criteria for our ongoing Phase 3 clinical trials of oral sulopenem and sulopenem may adversely affect our enrollment rates for patients in these clinical trials. In addition, we may face competition in enrolling suitable patients as a result of other companies conducting clinical trials for antibiotic product candidates that are intended to treat similar infections, resulting in slower than anticipated enrollment in our clinical trials. Enrollment delays in our clinical trials may result in increased development costs for oral sulopenem and sulopenem, or slow down or halt our product development for oral sulopenem and sulopenem.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or might require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, slow down or halt our product candidate development and approval process and jeopardize our ability to seek and obtain the marketing approval required to commence product sales and generate revenue, which would cause the value of our company to decline and limit our ability to obtain additional financing if needed. Furthermore, we rely on and expect to continue to rely on contract research organizations (CROs) and clinical trial sites to ensure the proper and timely conduct of our clinical trials, and we have limited influence over their performance.

***Success in non-clinical testing and early clinical trials does not ensure that later clinical trials will be successful, and we cannot assure our shareholders that any of our ongoing clinical trials or any other clinical trials that we may conduct will demonstrate consistent or adequate efficacy and safety to obtain regulatory approval to market our sulopenem program in any indication.***

Our ongoing Phase 3 clinical trials of oral sulopenem and sulopenem are subject to a number of specific risks arising from our clinical program and the design of such clinical trials.

We have not previously completed Phase 3 clinical trials of oral sulopenem or sulopenem in the indications uUTI, cUTI and cIAI, and we have not documented to the satisfaction of regulators that these treatments are effective in treating uUTIs, cUTIs or cIAIs in humans. Although we believe that oral sulopenem and sulopenem have the potential to treat uUTIs, cUTIs, and cIAIs in humans based on the results of prior preclinical studies and clinical trials, the results of these preclinical studies and clinical trials are not necessarily predictive of the results of our ongoing Phase 3 clinical trials, and we cannot guarantee that oral sulopenem and sulopenem will demonstrate the expected efficacy in clinical trial patients. We also cannot guarantee that the projections made from the pharmacokinetic and pharmacodynamic models that we developed from non-clinical and clinical oral sulopenem and sulopenem studies will be validated in our ongoing Phase 3 clinical trials.

Other companies in the pharmaceutical industry have frequently suffered significant setbacks in later clinical trials, even after achieving promising results in earlier non-clinical studies or clinical trials.

***Serious adverse events or undesirable side effects or other unexpected properties of oral sulopenem, sulopenem or any other product candidate may be identified during development or after approval that could delay, prevent or cause the withdrawal of regulatory approval, limit the commercial potential, or result in significant negative consequences following marketing approval.***

Serious adverse events or undesirable side effects caused by, or other unexpected properties of, our product candidates could cause us, an institutional review board (IRB), 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 oral sulopenem, sulopenem or any of our other product candidates is associated with serious or unexpected adverse events or undesirable side effects, the FDA or the IRBs at the institutions in which our studies are conducted, could suspend or terminate our clinical trials or the FDA or comparable foreign regulatory authorities could order us to cease clinical trials or deny approval of our product candidates for any or all targeted indications. Treatment-related side effects could also affect patient recruitment or the ability of enrolled patients to complete the clinical trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

While the active pharmaceutical ingredient in the bilayer tablet is sulopenem etzadroxil, the combination product with probenecid has not yet been tested extensively in patients. There may be unforeseen serious adverse events or side effects that differ from those seen in Phase 1 normal healthy volunteers with oral sulopenem or the prior post-marketing experience with probenecid. There may also be unexpected adverse events associated with probenecid that have not been seen to date. We may see higher rates of adverse events than were reported in the clinical trials Pfizer conducted in Japan.

To date, sulopenem and sulopenem etzadroxil have generally been well tolerated in clinical trials conducted in healthy subjects and patients. During the development of oral sulopenem and sulopenem, patients have experienced drug-related side effects including diarrhea, temporary increases in hepatic enzymes, allergic reactions, and rash. In the Japanese program, one patient reported a serious adverse event related to sulopenem of a transient elevation in liver function tests. The patient died due to metastatic lung cancer. Other serious adverse events recorded in patients receiving sulopenem in the Japanese program, which were not considered by the investigator to be related to sulopenem, included myocardial infarction with respiratory failure and progression of underlying ovarian carcinoma, in both cases resulting in death. For each of these patients, sulopenem was not determined to be the cause of death. If unexpected adverse events occur in any of our clinical trials, we may need to abandon development of our product candidates, or limit development to lower doses or to certain uses or subpopulations in which the undesirable side effects or other unfavorable 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 are later found to cause undesirable or unexpected side effects that prevent further development of the compound.

Undesirable side effects or other unexpected adverse events or properties of oral sulopenem, sulopenem or any of our other 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 clinical trials could be suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development of, or could deny approval of, oral sulopenem, sulopenem or other product candidates. If such an event occurs after such product candidates are approved, a number of potentially significant negative consequences may result, including:

- regulatory authorities may withdraw the approval of such product;
- we may be required to recall a product or change the way such product is administered to patients;
- 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;
- regulatory authorities may require the addition of a “black box” warning;
- we may be required to implement a Risk Evaluation and Mitigation Strategy (REMS), including the creation of 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;
- our product may become less competitive; and
- our reputation may suffer.

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

***Even if a product candidate does obtain regulatory approval, it may never achieve the market acceptance by physicians, patients, hospitals, third-party payors and others in the medical community that is necessary for commercial success, and the market opportunity may be smaller than we estimate.***

Even if we obtain FDA or other regulatory approvals and are able to launch oral sulopenem, sulopenem or any other product candidate commercially, the product candidate may not achieve market acceptance among physicians, patients, hospitals (including pharmacy directors) and third-party payors and, ultimately, may not be commercially successful. For example, physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Moreover, many antibiotics currently exist for the pathogens underlying uUTI, cUTI and cIAI. While many of those pathogens are resistant to certain drugs in the market, the selection is broad, and individual physicians' prescribing patterns vary widely and are affected by resistance rates in their geographies, whether their patients are at elevated risk, the ability of patients to afford branded drugs and concerns regarding generating resistance with specific classes of antibiotics.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If oral sulopenem, sulopenem or any other 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. Market acceptance of any product candidate for which we receive approval depends on a number of factors, including:

- the efficacy and safety of the product candidate as demonstrated in clinical trials as compared to alternative treatments;
- the potential and perceived advantages and disadvantages of the product candidates, including cost and clinical benefit relative to alternative treatments;
- relative convenience and ease of administration;
- the clinical indications for which the product candidate is approved;
- the willingness of physicians to prescribe the product;
- the willingness of hospital pharmacy directors to purchase the product for their formularies;
- acceptance by physicians, patients, operators of hospitals and treatment facilities and parties responsible for coverage and reimbursement of the product;
- the availability of coverage and adequate reimbursement by third-party payors and government authorities;
- the effectiveness of our sales and marketing efforts or those of collaborators, where we choose not to commercialize directly ourselves;
- the strength of marketing and distribution support;
- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling or an approved REMS;
- 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 approval of other new products for the same indications;
- the timing of market introduction of the approved product as well as competitive products;
- adverse publicity about the product or favorable publicity about competitive products;
- the emergence of bacterial resistance to the product; and
- the rate at which resistance to other drugs in the target infections grows.

In addition, the potential market opportunity for oral sulopenem and sulopenem is difficult to estimate. Our estimates of the potential market opportunity are predicated on several key assumptions such as industry knowledge and publications, 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 oral sulopenem and sulopenem could be smaller than our estimates of the potential market opportunity. If the actual market for oral sulopenem and sulopenem is smaller than we expect, or if the product fails to achieve an adequate level of acceptance by physicians, health care payors, patients, hospitals and others in the medical community, our product revenue may be limited and it may be more difficult for us to achieve or maintain profitability.

***We currently have no commercial organization. If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing oral sulopenem, sulopenem or any other product candidate if such product candidate is approved.***

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing oral sulopenem, sulopenem or any other product candidate if such product candidate is approved.

We are currently evaluating our commercialization strategy in the United States and other territories. We are focusing our initial commercial efforts on the United States market, which we believe represents the largest market opportunity for our sulopenem program. We currently do not have a sales, marketing or distribution infrastructure and we have no experience in the sales, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either build our marketing, sales, distribution, managerial and other non-technical capabilities, or make arrangements to outsource those functions to third parties. If oral sulopenem and sulopenem receive regulatory approval, we intend to build a commercial organization and recruit a targeted sales force with technical expertise, an internal marketing and health resource group, as well as a managed markets group focused on reimbursement activities with third-party payors and a specialty distribution team to ensure pharmacy-level stocking and, where we choose not to commercialize directly ourselves, we will seek to commercialize oral sulopenem and sulopenem through collaboration arrangements. The development of sales, marketing and distribution capabilities will require substantial resources, will be time-consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing and distribution capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization costs. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire a sales force in the United States that is sufficient in size or has adequate expertise in the medical markets that we intend to target. If we are unable to establish a sales force and marketing and distribution capabilities, our operating results may be adversely affected. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of our product candidates.

Factors that may inhibit our efforts to commercialize our products directly include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- our inability to identify the best territories to target based on resistance statistics and prescribers within those territories;
- the inability of a health resources group to obtain access to educate physicians regarding the attributes of our future 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; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

For those countries in which we choose not to commercialize directly ourselves, which may include the United States, we intend to use collaborators that have direct sales forces and established distribution systems to assist with the commercialization of oral sulopenem, sulopenem and any other product candidate. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues to us would likely be lower than if we were to directly market and sell products in those markets.

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 would have little control over such third parties, and any of them might 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 our product candidates.

***We face substantial competition from other pharmaceutical and biotechnology companies and our business 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 and biotechnology companies worldwide with respect to oral sulopenem, sulopenem and other product candidates that we may seek to develop and commercialize in the future. There are a number of pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of product candidates for the treatment of multi-drug resistant 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 oral sulopenem, sulopenem or any other product candidates that we may develop, which could render our product candidates obsolete and noncompetitive.

There are a variety of available oral therapies marketed for the treatment of multi-drug resistant infections that we would expect would compete with oral sulopenem and sulopenem, such as levofloxacin, ciprofloxacin, nitrofurantoin, fosfomycin, amoxicillin-clavulanate, cephalexin and trimethoprim-sulfamethoxazole. 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, for example in the fluoroquinolone class. If oral sulopenem or sulopenem is approved, the pricing may be at a significant premium over other competitive products that are generic. This may make it difficult for oral sulopenem or sulopenem to compete with these products.

There are also a number of oral product candidates in clinical development by third parties that are intended to treat UTIs. Some mid- to late-stage product candidates include ceftibuten clavulanate from Achaogen, Inc., tebipenem pivoxil from Spero Therapeutics, Inc., delafloxacin from Melinta Therapeutics, Inc., pivmecillinam from Utility Therapeutics Limited, ETX0282CPDP (a novel ß-lactamase inhibitor combined with cefpodoxime proxetil) from Entasis Therapeutics Holdings Inc. and omadacycline from Paratek Pharmaceuticals, Inc. If our competitors obtain marketing approval from the FDA or comparable foreign regulatory authorities for their product candidates more rapidly than us, it could result in our competitors establishing a strong market position before we are able to enter the market.

There are several IV-administered products marketed for the treatment of infections resistant to first-line therapy for gram-negative infections, including Avycaz from Allergan plc and Pfizer, Vabomere from Melinta Therapeutics, Inc., Zerbaxa from Merck & Co., Zemdri from Achaogen, Inc, and Xerava from Tetraphase Pharmaceuticals, Inc. There are also a number of IV-administered product candidates in late-stage clinical development that are intended to treat resistant gram-negative infections, including cefiderocol from Shionogi & Co. Ltd., Contepo from Nabriva Therapeutics plc (as successor to Zavante Therapeutics, Inc.) and imipenem-relabactam from Merck & Co.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products 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, management and sales and marketing 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 Generating Antibiotics Incentives Now Act (the GAIN Act). The GAIN Act is intended to provide incentives for the development of new, qualified infectious disease products (QIDP). One such incentive is that, once a product receives QIDP designation and completes the necessary clinical trials and is approved by the FDA, it will be given an additional five years of regulatory exclusivity regardless of whether it is protected by a patent, provided that it is already eligible for another type of regulatory exclusivity. The FDA has designated sulopenem and oral sulopenem as QIDPs for the indications of uUTI, cUTI and cIAI and, more recently, for the indications of community-acquired bacterial pneumonia, acute bacterial prostatitis, gonococcal urethritis, and pelvic inflammatory disease. Fast track designation for these seven indications in both the oral and intravenous formulations has also been granted. In December 2016, the Cures Act was passed, providing additional support for the development of new 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 product candidates that could be competitive with oral sulopenem, sulopenem and our other product candidates.

***Even if we are able to commercialize oral sulopenem, sulopenem or any other product candidate, the product may become subject to unfavorable pricing regulations, or third-party payor coverage and reimbursement policies that could harm our business.***

Marketing approvals, pricing, coverage and reimbursement for new drug products vary widely from country to 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 licensing 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 affect the revenues that 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.

The commercial success of oral sulopenem and any future product candidates, if approved, will depend substantially, both in the United States and outside the United States, on the extent to which coverage and adequate reimbursement for the product and related treatments are available from government health programs, private health insurers and other third-party payors. If coverage is not available, or reimbursement is limited, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investments. Government authorities and third-party payors, such as health insurers and managed care organizations, publish formularies that identify the medications they will cover and the related payment levels. The healthcare industry is focused on cost containment, both in the United States and elsewhere. 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.

In the United States, sales of our product candidates 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. There is no uniform coverage and reimbursement policy among third-party payors; however, private third-party payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Obtaining coverage and reimbursement approval for a product candidate from third-party payors is a time-consuming and costly process that may require the provision of supporting scientific, clinical and cost effectiveness data for the use of such product candidate to the third-party payor. There may be significant delays in obtaining such coverage and reimbursement for newly approved products, and coverage may be more limited than the purposes for which the product candidate is approved by the FDA. Moreover, eligibility for coverage and reimbursement does not imply that a product candidate will be paid for in all cases or at a rate that covers operating costs, including research, development, intellectual property, manufacture, sales and distribution expenses. Reimbursement rates may vary according to the use of the product candidate and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost products and may be incorporated into existing payments for other services. It is difficult to predict what third-party payors will decide with respect to coverage and reimbursement for our product candidates.

We currently expect that sulopenem IV, if approved, will be administered in a hospital setting, and oral sulopenem, if approved, will be used in a community setting and possibly be administered in a hospital inpatient setting as well. In the United States, third-party payors generally reimburse hospitals a single bundled payment established on a prospective basis intended to cover all items and services provided to the patient during a single hospitalization. Hospitals bill third-party payors for all or a portion of the fees associated with the patient's hospitalization and bill patients for any deductibles or co-payments. Because there is typically no separate reimbursement for drugs administered in a hospital inpatient setting, some of our target customers may be unwilling to adopt our product candidates in light of the additional associated cost. If we are forced to lower the price we charge for our product candidates, if approved, our gross margins may decrease, which would adversely affect our ability to invest in and grow our business.

An inability to promptly obtain coverage and adequate payment rates from third-party payors for any approved product candidates 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.

***We cannot predict whether bacteria may develop resistance to oral sulopenem or sulopenem, which could affect their revenue potential.***

We are developing oral sulopenem and sulopenem to treat drug-resistant bacterial infections. The bacteria responsible for these infections evolve quickly and readily transfer their resistance mechanisms within and between species. We cannot predict whether or when bacterial resistance to oral sulopenem and sulopenem may develop.

As with some commercially available carbapenems, oral sulopenem and sulopenem are not active against organisms expressing a resistance mechanism mediated by enzymes known as carbapenemases. Although occurrence of this resistance mechanism is currently uncommon, we cannot predict whether carbapenemase-mediated resistance will become widespread in regions where we

intend to market sulopenem if it is approved. The use of carbapenems orpenems in areas with drug-resistant infections or in countries with poor public health infrastructures, or the potentially extensive use of oral sulopenem or sulopenem outside of controlled hospital settings or in the community, could contribute to the rise of resistance. In addition, prescribers may be less likely to prescribe oral sulopenem and sulopenem if they are concerned about contributing to the rise of antibiotic resistance. If resistance to oral sulopenem or sulopenem becomes prevalent, or concerns about such resistance are strong, our ability to generate revenue from oral sulopenem and sulopenem could suffer.

***We may be subject to costly product liability claims related to our clinical trials and product candidates and, if we are unable to obtain adequate insurance or are required to pay for liabilities resulting from a claim excluded from, or beyond the limits of our insurance coverage, a material liability claim could adversely affect our financial condition.***

Because we conduct clinical trials with human patients, we face the risk that the use of our product candidates may result in adverse side effects to patients in our clinical trials. We face even greater risks upon any commercialization of our product candidates. Although we have product liability insurance, which covers our clinical trials for up to $20.0 million, our insurance may be insufficient to reimburse us for any expenses or losses we may suffer. We will need to increase our insurance coverage if and when we receive marketing approval for and begin selling oral sulopenem, sulopenem or any other product candidate. We do not know whether we will be able to continue to obtain product liability coverage and obtain expanded coverage if we require it, on acceptable terms, if at all.

We may not have sufficient resources to pay for any liabilities resulting from a claim excluded from, or beyond the limits of, our insurance coverage. Where we have provided indemnities in favor of third parties under our agreements with them, there is also a risk that these third parties could incur a liability and bring a claim under such indemnities. An individual may bring a product liability claim against us alleging that one of our product candidates or products causes, or is claimed to have caused, an injury or is found to be unsuitable for consumer use. Any product liability claim brought against us, with or without merit, could result in:

- withdrawal of clinical trial volunteers, investigators, patients or trial sites;
- the inability to commercialize our product candidates;
- decreased demand for our product candidates;
- regulatory investigations that could require costly recalls or product modifications;
- loss of revenue;
- substantial costs of litigation;
- liabilities that substantially exceed our product liability insurance, which we would then be required to pay ourselves;
- an increase in our product liability insurance rates or the inability to maintain insurance coverage in the future on acceptable terms, if at all;
- the diversion of management’s attention from our business; and
- damage to our reputation and the reputation of our products.

***Our operations, including our use of hazardous materials, chemicals, bacteria and viruses, require us to comply with regulatory requirements and expose us to significant potential liabilities.***

Our operations involve the use of hazardous materials, including chemicals, and may produce dangerous waste products. Accordingly, we, along with the third parties that conduct clinical trials and manufacture our products and product candidates on our behalf, are subject to federal, state, local and foreign laws and regulations that govern the use, manufacture, distribution, storage, handling, exposure, disposal and recordkeeping with respect to these materials. We are also subject to a variety of environmental and occupational health and safety laws. Compliance with current or future laws and regulations can require significant costs and we could be subject to substantial fines and penalties in the event of non-compliance. In addition, the risk of contamination or injury from these materials cannot be completely eliminated. In such event, we could be held liable for substantial civil damages or costs associated with the cleanup of hazardous materials.

***If we experience a significant disruption in our information technology systems or breaches of data security, our business could be adversely affected.***

We rely on information technology systems to keep financial records, capture laboratory data, maintain clinical trial data and corporate records, communicate with staff and external parties and operate other critical functions. Our information technology systems are potentially vulnerable to disruption due to breakdown, malicious intrusion and computer viruses or other disruptive events

including, but not limited to, natural disaster. If we were to experience a prolonged system disruption in our information technology systems or those of certain of our vendors, it could delay or negatively impact the development and commercialization of our sulopenem program and any future product candidates or technology, which could adversely impact our business. Although we maintain offsite back-ups of our data, if operations at our facilities were disrupted, it may cause a material disruption in our business if we are not capable of restoring function on an acceptable timeframe. In addition, our information technology systems are potentially vulnerable to data security breaches—whether by employees or others—which may expose sensitive data to unauthorized persons. Such data security breaches could lead to the loss of trade secrets or other intellectual property or, could lead to the public exposure of personal information (including sensitive personal information) of our employees and others, any of which could have a material adverse effect on our business, financial condition and results of operations. Moreover, a security breach or privacy violation that leads to disclosure or modification of, personally identifiable information, could harm our reputation, compel us to comply with applicable European, and United States federal and/or state, breach notification laws, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to litigation and liability under laws and regulations that protect personal data, resulting in increased costs or loss of revenue. In addition, a data security breach could result in loss of clinical trial data or damage to the integrity of that data. If we are unable to prevent such security breaches or privacy violations or implement satisfactory remedial measures, our operations could be disrupted, and we may suffer reputational damage, financial loss and other negative consequences because of lost or misappropriated information. In addition, these breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above.

**Risks Related to Our Dependence on Third Parties**

***If we fail to comply with our obligations in our agreement with Pfizer, we could lose such rights that are important to our business.***

We rely heavily on the Pfizer License pursuant to which we exclusively in-license certain patent rights and know-how related to sulopenem etzadroxil and certain know-how related to the IV formulation of sulopenem. The Pfizer License imposes diligence, development and commercialization timelines, milestone payments, royalties, insurance and other obligations on us, and we may enter into additional agreements, including license agreements, with other parties in the future which impose similar obligations.

The Pfizer License gives us exclusive worldwide rights to develop, manufacture, and commercialize sulopenem etzadroxil and sulopenem, or any other prodrug of sulopenem previously identified by Pfizer as well as the right to use relevant information and regulatory documentation developed by Pfizer to support any regulatory filing worldwide. In exchange for those rights, we are obligated to satisfy diligence requirements, including using commercially reasonable efforts to develop, obtain regulatory approval for and commercialize sulopenem etzadroxil and sulopenem by implementing a specified development plan and providing an update on progress on an annual basis. Under the Pfizer License, we paid Pfizer a one-time non-refundable upfront fee of $5.0 million, clinical milestone payments totaling $15.0 million, upon first patient dosing of oral sulopenem and sulopenem in a Phase 3 clinical trial, and are obligated to pay Pfizer milestone payments upon the achievement of other specified regulatory and sales milestones as well as royalties ranging from a single-digit to mid-teens percentage based on the amount of marginal net sales of each licensed product. Pfizer also received 381,922 of our Series A preferred shares (which converted to ordinary shares in connection with our IPO) as additional payment for the licensed rights.

If we fail to comply with our obligations to Pfizer under the Pfizer License, Pfizer may have the right to terminate the Pfizer License, in which event we would not be able to develop, obtain regulatory approval for, manufacture or market any product candidate that is covered by the Pfizer License, including sulopenem etzadroxil and sulopenem, which would materially harm our business, financial condition, results of operations and growth prospects. Any termination of the Pfizer License or reduction or elimination of our rights thereunder may result in our having to negotiate new or reinstated agreements with less favorable terms. Any termination of the Pfizer License would cause us to lose our rights to important intellectual property or technology.

***We expect to depend on collaborations with third parties for the development and commercialization of oral sulopenem and sulopenem in certain territories. Our prospects with respect to those product candidates will depend in part on the success of those collaborations.***

Although we are focusing our initial commercial efforts on the United States market, which we believe represents the largest market opportunity for our sulopenem program, we are also evaluating our commercialization strategy both within and outside the United States. For those countries in which we choose not to commercialize directly ourselves, we intend to seek to commercialize oral sulopenem and sulopenem through collaboration arrangements. In addition, we may seek third-party collaborators for development and commercialization of other product candidates in the United States and other territories. 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 but plan to initiate discussions with potential commercial partners.

We may derive revenue from research and development fees, license fees, milestone payments and royalties underany collaborative arrangement into which we enter. Our ability to generate revenue 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 candidate that we license to a third party.

We face significant competition in seeking and obtaining appropriate collaborators. Collaborations involving our product candidates 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;
- collaborators may not pursue development and commercialization of our 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;
- a collaborator 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 product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time consuming and expensive;
- collaborators may not properly maintain, defend or enforce 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, misappropriate or otherwise violate 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 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 candidate licensed to it by us.

***We rely on third parties to conduct our preclinical studies and our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may be unable to obtain regulatory approval for or commercialize any of our product candidates. If they do not perform satisfactorily, our business may be materially harmed.***

We do not independently conduct non-clinical studies that comply with good laboratory practice (GLP) requirements. We also do not have the ability to independently conduct clinical trials of any of our product candidates. We rely on third parties, such as CROs, clinical data management organizations, medical institutions, and clinical investigators to conduct our clinical trials of oral sulopenem and sulopenem and expect to rely on these third parties to conduct clinical trials of any potential product candidates. 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 CRO for a clinical 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 clinical trial. While we will have agreements governing their activities, we control only certain aspects of their activities and have limited influence over their actual performance. The third parties with whom we contract for execution of our GLP studies and our clinical trials play a significant role in the conduct of these studies and clinical trials and the subsequent collection and analysis of data. Although we rely on these third parties to conduct our GLP-compliant non-clinical studies and clinical trials, we remain responsible for ensuring that each of our non-clinical studies and clinical trials are conducted in accordance with applicable laws and regulations, and our reliance on the CROs does not relieve us of our regulatory responsibilities. The FDA and regulatory authorities in other jurisdictions also require us to comply with standards, commonly referred to as good clinical practices (GCPs), for conducting, monitoring, recording and reporting the results of clinical trials to assure that data and reported results are accurate and that the trial subjects are adequately informed of the potential risks of participating in clinical trials. The FDA enforces these GCPs 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 GCPs, 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 assure our shareholders that, upon inspection, the FDA will determine that any of our clinical trials comply with GCPs. 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 may 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 oral sulopenem, sulopenem or other product candidates could be harmed, our costs could increase and our ability to generate revenue 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 contract with third parties for the manufacture of preclinical and clinical supplies of oral sulopenem and sulopenem and expect to continue to do so in connection with any future commercialization and for any future clinical trials and commercialization of our product candidates and potential product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.***

We do not have the internal infrastructure or capability to manufacture oral sulopenem and sulopenem for use in the conduct of our preclinical research or clinical trials. We rely on third-party contract manufacturers to manufacture supplies of oral sulopenem and sulopenem, and we expect to rely on third-party contract manufacturers to manufacture commercial quantities of any product candidate that we commercialize following approval for marketing by applicable regulatory authorities, if any. Reliance on third-party manufacturers entails risks, including:

- manufacturing delays if our third-party manufacturers give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of their agreement with us;
- 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 delays in identifying or qualifying replacements.

We will enter into agreements with third-party contract manufacturers for the commercial production of oral sulopenem and sulopenem. 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 current Good Manufacturing Practices, or 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 approved by the FDA after we submit an NDA and before potential approval of the product candidate. Similar regulations apply to manufacturers of our product candidates for use or sale in countries outside of the United States. We have no direct control over the ability of our third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel, 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 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. 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, 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 effect on our business, financial condition and results of operations.

We and our third-party suppliers also continue to refine and improve the manufacturing process, certain aspects of which are complex and unique, and we may encounter difficulties with new or existing processes, particularly as we seek to significantly increase our capacity to commercialize oral sulopenem and sulopenem. Our reliance on contract manufacturers also exposes us to the possibility that they, or third parties with access to their facilities, will have access to and may appropriate our trade secrets or other proprietary information.

As drug candidates are developed through non-clinical studies to late-stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, methods of making drug formulations, and drug formulations, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our drug candidates to perform differently and affect the results of clinical trials or other future clinical trials conducted with the altered materials. Such changes may also require additional testing, FDA notification or FDA approval. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our drug candidates and jeopardize our ability to commence sales and generate revenue.

Our current and anticipated future dependence upon others for the manufacture of oral sulopenem and sulopenem and any future product candidates may adversely affect our future profit margins and our ability to commercialize any products for which we receive marketing approval on a timely and competitive basis.

**Risks Related to Our Intellectual Property**

***We rely heavily on the Pfizer License for the patent rights and know-how required to develop and commercialize oral sulopenem and the know-how required to develop the IV formulation of sulopenem.***

We currently do not own any patents and rely heavily on the Pfizer License for intellectual property rights that are important or necessary for the development of oral sulopenem and sulopenem. We do not own or license any patent rights that cover the IV formulation of sulopenem. In addition, all patents directed to the compound sulopenem expired prior to us entering into the Pfizer License. Licenses to additional third-party intellectual property, technology and materials that may be required for the development and commercialization of our sulopenem program or any other product candidates or technology may not be available at all or on commercially reasonable terms. In that event, we may be required to expend significant time and resources to redesign our sulopenem program and any other product candidates or technology we may obtain in the future or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize oral sulopenem or sulopenem or other future product candidates or technologies, which could materially harm our business, financial condition, results of operations and growth prospects.

Under the Pfizer License, and we expect under certain of our future license agreements, we are responsible for prosecution and maintenance of the licensed patents and for bringing any actions against any third party for infringing on such patents. In addition, the Pfizer License requires, and we expect certain of our future license agreements would also require, us to meet certain development

thresholds to maintain the license, including establishing a set timeline for developing and commercializing products. In addition, such license agreements are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and growth prospects. Disputes may arise regarding intellectual property subject to the Pfizer License or any of our future license agreements, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe, misappropriate or otherwise violate any intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under the license agreement;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

In spite of our best efforts, Pfizer and any potential future licensors might conclude that we have materially breached our license agreements and might therefore terminate the relevant license agreements, thereby removing our ability to develop and commercialize products and technology covered by such license agreements. If any of our inbound license agreements are terminated, or if the underlying patents fail to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products identical to ours. This could have a material adverse effect on our competitive position, business, financial condition, results of operations and growth prospects.

***If we are unable to obtain and maintain patent protection or other intellectual property rights for oral sulopenem or our other technology and product candidates, or if the scope of the patent protection or intellectual property rights we obtain is not sufficiently broad, we may not be able to successfully develop or commercialize oral sulopenem or any other product candidates or technology or otherwise compete effectively in our markets.***

We rely upon a combination of patents, trademarks, trade secret protection, confidentiality agreements and other proprietary rights to protect the intellectual property related to our development programs and product candidates. Our success depends, in part, on obtaining and maintaining patent protection and successfully enforcing these patents and defending them against third-party challenges in the United States and other countries. If we or our licensors are unable to obtain or maintain patent protection with respect to oral sulopenem or any other product candidates or technology we develop, our business, financial condition, results of operations and growth prospects could be materially harmed.

We have sought to protect our proprietary position by in-licensing patents in the United States and abroad related to oral sulopenem. The patent prosecution process is expensive and time-consuming, and we and our licensors may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner or in all jurisdictions. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Moreover, although we control prosecution of the patents we have licensed from Pfizer related to our sulopenem program, we may not always have the right to control the preparation, filing and prosecution of patent applications, or to maintain, enforce or defend the patents, covering technology that we may license from third parties. Therefore, these patents and patent applications may not be prosecuted, maintained, enforced or defended in a manner consistent with the best interests of our business. The patent applications that we may own in the future or in-license may fail to result in issued patents with claims that cover our current and future product candidates in the United States or in other countries. Patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless, and until, a patent issues from such applications, and then only to the extent the issued claims cover the technology.

If any patent applications we may in-license in the future with respect to our development programs or product candidates fail to issue, if their breadth or strength of protection is threatened or if they fail to provide meaningful exclusivity for our current and future product candidates, it could dissuade companies from collaborating with us to develop product candidates and threaten our ability to commercialize products. Any such outcome could materially harm our competitive position, business, financial condition, results of operations and growth prospects.

The patent position of pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, the laws of countries outside the United States may not protect our

rights to the same extent as the laws of the United States. For example, EU patent law restricts the patentability of methodsof treatment of the human body more than U.S. law does. In addition, publications of discoveries in scientific literature often lag behind the actual discoveries, patent applications in the United States and other jurisdictions remain confidential for a period after filing, and some remain so until issued. Therefore, we cannot know with certainty whether we were the first to make the inventions claimed in the patents or pending patent applications we currently own, license or may own or license in the future, or that we were the first to file for patent protection of such inventions. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. There is no assurance that all potentially relevant prior art relating to our patent rights has been found, and such prior art could potentially invalidate one or more of the patents we currently license or may own or license in the future or prevent a patent from issuing from one or more pending patent applications we may own or license in the future. There is also no assurance that prior art of which we are aware, but which we do not believe affects the validity or enforceability of a claim in our patent rights, may, nonetheless, ultimately be found to affect the validity or enforceability of a claim. Even if patents do successfully issue and even if such patents cover our current and future product candidates, third parties may challenge their ownership, validity, enforceability or scope, which may result in such patents being narrowed, invalidated or held unenforceable, which could allow third parties to commercialize our technology or products 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. Any successful opposition to these patents or any other patents owned by us in the future or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Furthermore, even if they are unchallenged, our patents rights may not adequately protect our product candidates and technology, provide exclusivity for our product candidates, prevent others from designing around our claims or provide us with a competitive advantage. Any of these outcomes could impair our ability to prevent competition from third parties. Changes in either the patent laws or interpretation of the patent laws in the United States or other countries may diminish the value of our patent rights or narrow the scope of our patent protection.

We cannot offer any assurances about whether any issued patents will be found invalid and unenforceable or will be challenged by third parties. Any successful challenge or opposition to patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced.

Furthermore, our patent rights may be subject to a reservation of rights by one or more third parties. For example, certain research we conducted was funded in part by the U.S. government. As a result, the U.S. government may have certain march-in rights to patents and technology arising out of such research, if any. When new technologies are developed with government funding, the government generally obtains certain rights in any resulting patents, including a non-exclusive license authorizing the government to use the invention. These rights may permit the government to disclose our confidential information to third parties and to exercise march-in rights to use or allow third parties to use our licensed technology. The government can exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the government-funded technology, to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to U.S. industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States. Any exercise by the government of such rights could harm our competitive position, business, financial condition, results of operations and growth prospects. For example, under the CARB-X grant funding program, the U.S. Department of Health and Human Services (HHS) awarded us a grant in connection with research to reduce the threat to human health from antimicrobial resistance and we granted the U.S. government a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the U.S. government any inventions arising out of our research globally. In addition, under such agreement, if we or our licensees do not use commercially reasonable efforts to exploit or further the development of any intellectual property rights we have generated out of such research within five years of the end date of our research project, Wellcome Trust Limited has the option to take responsibility for the commercialization and exploitation of such intellectual property rights, including by way of sale, assignment and license of such intellectual property rights.

***We may not identify relevant third-party patents or may incorrectly interpret the relevance, scope or expiration of a third party patent which might adversely affect our ability to develop and market our product candidates.***

We cannot guarantee that any of our or our licensors' patent searches or analyses, including but not limited to the identification of relevant patents, the scope of patent claims or the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. For example, U.S. applications filed before November 29, 2000 and certain U.S. applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Patent applications in the United States and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our product candidates could have been filed by others without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our product candidates or the use of our product candidates. The scope of a patent claim is determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a

pending application may be incorrect, which may negatively impact our ability to market our product candidates. We may incorrectly determine that our product candidates are not covered by a third-party patent or may incorrectly predict whether a third party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States or abroad that we consider relevant may be incorrect, which may negatively impact our ability to develop and market our product candidates. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our product candidates.

***The patent protection for our product candidates may expire before we are able to maximize their commercial value which may subject us to increased competition and reduce or eliminate our opportunity to generate product revenue.***

Patents have a limited lifespan. In the United States, if all maintenance fees are paid timely, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. The patents for our product candidates have varying expiration dates and, if these patents expire, we may be subject to increased competition and we may not be able to recover our development costs. For example, our licensed U.S. patent claim for a composition of matter patent for oral sulopenem is due to expire in 2029, subject to potential extension to 2034 under the Drug Price Competition and Patent Term Restoration Act of 1984 (referred to as the Hatch-Waxman Act). Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our patent rights may not provide us with sufficient rights to exclude others from commercializing product candidates similar or identical to ours.

The FDA designated sulopenem and oral sulopenem as QIDPs for the indications of uUTI, cUTI and cIAI and, more recently, for the indications of community-acquired bacterial pneumonia, acute bacterial prostatitis, gonococcal urethritis, and pelvic inflammatory disease. Fast track designation for these seven indications in both the oral and intravenous formulations has also been granted. QIDP status provides the potential for a more rapid review cycle for an NDA and could add five years to any regulatory exclusivity period that we may be granted. However, that does not guarantee that we will receive any regulatory exclusivity or that any such exclusivity will be for a period sufficient to provide us with any commercial advantage. Moreover, we do not own or license any patent directed to the compound sulopenem.

Depending upon the timing, duration and conditions of FDA marketing approval of our product candidates, one or more of the U.S. patents we currently license may be eligible for limited patent term extension under the Hatch-Waxman Act, and similar legislation in the European Union. The Hatch-Waxman Act permits a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. We may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of the relevant patents or otherwise fail to satisfy applicable requirements and the length of the extension could be less than we request. To the extent we wish to pursue patent term extension based on a patent that we in-license from Pfizer or another third party, we would need the cooperation of Pfizer or the third party. Moreover, similar extensions may be available in some of the larger economic territories but may not be available in all of our markets of interest.

If we are unable to obtain patent term extension/restoration or some other exclusivity, or the term of any such extension is less than we request, the period during which we can enforce our exclusive rights for that product will be shortened and our competitors may obtain approval to market competing products sooner. As a result, we could be subject to increased competition and our opportunity to establish or maintain product revenue could be substantially reduced or eliminated. Furthermore, we may not have sufficient time to recover our development costs prior to the expiration of our U.S. and non-U.S. patent rights. If this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case. Any of the foregoing would materially harm our business, financial condition, results of operations and growth prospects.

***Intellectual property rights do not necessarily address all potential threats to our business.***

Once granted, patents may remain open to opposition, interference, re-examination, post-grant review, *inter partes* review, nullification or derivation action in court or before patent offices or similar proceedings for a given period after allowance or grant, during which time third parties can raise objections against such grant. In the course of such proceedings, which may continue for a protracted period of time, the patent owner may be compelled to limit the scope of the allowed or granted claims thus attacked, or may lose the allowed or granted claims altogether. In addition, the degree of future protection afforded by our intellectual property rights is uncertain because even granted intellectual property rights have limitations, and may not adequately protect our business. The following examples are illustrative:

- others may be able to make compounds or formulations that are similar to oral sulopenem and sulopenem compounds or formulations but that are not covered by the claims of our patent rights;
- the patents of third parties may have an adverse effect on our business;
- we or our licensors or any future strategic partners might not have been the first to conceive or reduce to practice the inventions covered by the issued patents that we own or have exclusively licensed;
- we or our licensors or any future strategic partners might not have been the first to file patent applications covering certain of our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible any pending patent applications will not lead to issued patents;
- issued patents that we may own in the future or have exclusively licensed may not provide us with any competitive advantage, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- third parties performing manufacturing or testing for us using our product candidates or technologies could use the intellectual property of others without obtaining a proper license; and
- we may not develop additional proprietary technologies that are patentable.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

***Changes in patent laws or patent jurisprudence could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.***

As is the case with other pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the pharmaceutical industry involves both technological complexity and legal complexity. Therefore, obtaining and enforcing pharmaceutical patents is costly, time-consuming and inherently uncertain. In addition, the America Invents Act (the AIA) was signed into law on September 16, 2011, and many of its substantive changes became effective on March 16, 2013.

An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned to a “first-to-file” system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. A third party that files a patent application in the U.S. Patent and Trademark Office, or USPTO, after that date but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by the third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application, but circumstances could prevent us from promptly filing patent applications on our inventions.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and providing opportunities for third parties to challenge any issued patent in the USPTO, including through post-issuance patent review procedures such as *inter partes* review, post-grant review and covered business methods. This applies to all U.S. patents, including those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO

procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. The AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

In the last few years, the USPTO has developed regulations and procedures to govern administration of the AIA, and many of the substantive changes to patent law associated with the AIA, in particular, the first to file provisions only became effective on March 16, 2013. Accordingly, it is not clear what, if any, impact the AIA will have on the operation of our business and this may not be known until such time as we, or our licensors or collaboration partners, are filing patent applications for an invention or seeking to defend issued patents. However, the AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our or our licensors' or collaboration partners' patent applications and the enforcement or defense of our or our licensors' or collaboration partners' issued patents, all of which could have an adverse effect on our business and financial condition.

Moreover, the standards that the USPTO and foreign patent offices use to grant patents are not always applied predictably or uniformly and can change. Consequently, any patents we currently license or may own or license in the future may have a shorter patent term than expected or may not contain claims that will permit us to stop competitors from using our technology or similar technology or from copying our products. Similarly, the standards that courts use to interpret patents are not always applied predictably or uniformly and may evolve, particularly as new technologies develop. In addition, changes to patent laws in the United States or other countries may be applied retroactively to affect the ownership, validity, enforceability or term of patents we currently license or may own or license in the future.

For example, the U.S. Supreme Court's rulings on several patent cases in recent years, such as *Association for Molecular Pathology v. Myriad Genetics, Inc*., *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, and *Alice Corporation Pty. Ltd. v. CLS Bank International*, either narrow the scope of patent protection available in certain circumstances or weaken the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. Similarly, the complexity and uncertainty of European patent laws has also increased in recent years. In addition, the European patent system is relatively stringent in the type of amendments that are allowed during prosecution. These changes could limit our ability to obtain new patents in the future that may be important for our business.

***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, misappropriate or otherwise violate our patents, trademarks, copyrights or other intellectual property or those of our licensors. To counter infringement, misappropriation, unauthorized use or other violations, we may be required to file legal claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. We may not be able to prevent, alone or with our licensors, infringement, misappropriation or other violations of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States. 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, misappropriation or other intellectual property 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.

***Third parties may initiate legal proceedings alleging that we are infringing, misappropriating or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could have a negative impact on the success of our business.***

Our commercial success depends, in part, upon our ability, and the ability of our future collaborators, to develop, manufacture, market and sell oral sulopenem, sulopenem and any future product candidates, if approved, and use our proprietary technologies without alleged or actual infringement, misappropriation or other violation of the patents and other intellectual property rights of third parties. There have been many lawsuits and other proceedings involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and reexamination proceedings before the USPTO and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates. Some claimants may have substantially greater resources than we do and may be able to sustain the costs of complex intellectual property litigation to a greater degree and for longer periods of time than we could. In addition, patent holding companies that focus solely on extracting royalties and settlements by enforcing patent rights may target us. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the intellectual property rights of third parties.

We may in the future become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to oral sulopenem, sulopenem or any future product candidates and technology, including interference or derivation proceedings, post grant review and *inter partes* review before the USPTO or similar adversarial proceedings or litigation in other jurisdictions. Similarly, we or our licensors or collaborators may initiate such proceedings or litigation against third parties, e.g., to challenge the validity or scope of intellectual property rights controlled by third parties. In order to successfully challenge the validity of any U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court would invalidate the claims of any such U.S. patent. Moreover, third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, and the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire or are finally determined to be invalid or unenforceable. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our compositions, formulations, or methods of treatment, prevention or use, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtained a license or until such patent expires or is finally determined to be invalid or unenforceable. In either case, such a license may not be available on commercially reasonable terms, or at all. Even if we were able to obtain a license, it could be nonexclusive, thereby giving our competitors access to the same technologies licensed to us. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In such an event, we would be unable to further practice our technologies or develop and commercialize any of our product candidates at issue, which could harm our business significantly.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates, if approved. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of management and employee time and resources from our business. Third parties making such claims may have the ability to dedicate substantially greater resources to these legal actions than we or our licensors or collaborators can. In the event of a successful claim of infringement, misappropriation or other violation against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure.

There has been substantial litigation and other proceedings regarding patent and other intellectual property rights in the pharmaceutical and biotechnology industries. In addition to infringement claims against us, we may become a party to other patent litigation and other adversarial proceedings such as proceedings before the Patent Trial and Appeal Board and opposition proceedings in the European Patent Office regarding intellectual property rights with respect to our products and technology.

Patent litigation and other proceedings may also absorb significant management time. The cost to us of any patent litigation or other proceeding, even if resolved in our favor, could be substantial. During the course of any patent or other intellectual property litigation or other proceeding, there could be public announcements of the results of hearings, rulings on motions, and other interim proceedings or developments and if securities analysts or investors regard these announcements as negative, the perceived value of our product candidates or intellectual property could be diminished. Accordingly, the market price of our ordinary shares may decline. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our business, ability to compete in the marketplace, financial condition, results of operations and growth prospects.

***We may not be able toprotect our intellectual property rights globally, which could negatively impact our business.***

Filing, prosecuting and defending patents covering oral sulopenem, sulopenem and any future product candidates globally would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Further, licensing partners may not prosecute patents in certain jurisdictions in which we may obtain commercial rights, thereby precluding the possibility of later obtaining patent protection in these countries. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and may also export infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and any future patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license. Furthermore, while we intend to protect our intellectual property rights in our expected significant markets, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our product candidates. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate, which may have an adverse effect on our ability to successfully commercialize our product candidates in all of our expected significant foreign markets.

Additionally, the requirements for patentability may differ in certain countries, particularly developing countries. For example, unlike other countries, China has a heightened requirement for patentability, and specifically requires a detailed description of medical uses of a claimed drug. In India, unlike the United States, there is no link between regulatory approval of a drug and its patent status. Furthermore, generic or biosimilar drug manufacturers or other competitors may challenge the scope, validity or enforceability of our or our licensors' patents, requiring us or our licensors to engage in complex, lengthy and costly litigation or other proceedings. Generic or biosimilar drug manufacturers may develop, seek approval for, and launch biosimilar versions of our products. In addition, certain countries in Europe and developing countries, including China and India, have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In those countries, we and our licensors may have limited remedies if patents are infringed or if we or our licensors are compelled to grant a license to a third party, which could materially diminish the value of those patents. This could limit our potential revenue opportunities. Accordingly, our and our licensors' efforts to enforce intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license.

***We may be subject to claims that we or our employees, consultants, contractors or advisors have infringed, misappropriated or otherwise violated 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, know-how or trade secrets 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, we may in the future be subject to claims that former employees, collaborators or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. 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. To the extent that we fail to obtain such assignments, such assignments do not contain a self-executing assignment of intellectual property rights 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. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. 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.

***Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.***

Periodic maintenance and annuity fees on any issued patent are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent. The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents covering our products, our competitors might be able to enter the market, which would have a material adverse effect on our business, financial condition, results of operations and growth prospects.

***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 and products, 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 employees, 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. We also seek to preserve the integrity and confidentiality of our data, trade secrets and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. We cannot guarantee that our trade secrets and other proprietary and confidential information will not be disclosed or that competitors will not otherwise gain access to our trade secrets. Any party with whom we have 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, some courts both within and outside the United States may be less willing or unwilling to protect trade secrets. Further, 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.

Trade secrets and know-how can be difficult to protect as trade secrets and know-how will over time be disseminated within the industry through independent development, the publication of journal articles, and the movement of personnel skilled in the art from company to company or academic to industry scientific positions. If we fail to prevent material disclosure of the know-how, trade secrets and other intellectual property related to our technologies to third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition. Even if we are able to adequately protect our trade secrets and proprietary information, our trade secrets could otherwise become known or could be independently discovered by our competitors. For example, competitors could purchase our products and attempt to replicate some or all of the competitive advantages we derive from our development efforts, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, in the absence of patent protection, we would have no right to prevent them, or those to whom they communicate, from using that technology or information to compete with us.

We may not be able to prevent misappropriation of our intellectual property, trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the United States. 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 this type of litigation.

***We have not yet registered our trademarks in certain jurisdictions. Failure to secure those registrations could adversely affect our business.***

We have registered trademarks for "Iterum" in the United States, European Union, Japan, Switzerland and Canada. If we are unable to secure registrations for our trademarks in other countries, we may encounter more difficulty in enforcing them against third parties than we otherwise would, which could adversely affect our business. We have also not yet registered trademarks for any of our product candidates in any jurisdiction. Any trademark applications we may file for our product candidates are not guaranteed to be allowed for registration, and even if they are, we may fail to maintain or enforce such registered trademarks. During trademark registration proceedings in the United States and other jurisdictions, we may receive rejections. We are given an opportunity to respond to those rejections, but we may not be able to overcome such rejections. In addition, in the USPTO and in comparable agencies in many other jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings.

In addition, any proprietary name we propose to use with oral sulopenem, sulopenem or any other product candidate in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable proprietary product name that would qualify under applicable trademark laws, not infringe, misappropriate or otherwise violate the existing rights of third parties and be acceptable to the FDA and the EMA.

Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our business, financial condition, results of operations and growth prospects.

**Risks Related to Regulatory Approval and Other Legal Compliance Matters**

***If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize oral sulopenem, sulopenem or other future product candidates, and our ability to generate revenue will be materially impaired.***

Our product candidates, oral sulopenem and sulopenem, and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, 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 a product candidate will prevent us from commercializing the product candidate. We currently do not have any products approved for sale in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations to assist us in this process.

Although we have QIDP status and fast track designation for sulopenem and oral sulopenem for the indications of uUTI, cUTI and cIAI (and, more recently, for the indications of community-acquired bacterial pneumonia, acute bacterial prostatitis, gonococcal urethritis, and pelvic inflammatory disease) which may provide for a more rapid new drug application review cycle, the time required to obtain approval, if any, by the FDA and comparable foreign authorities is unpredictable and typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval. Neither we nor any future collaborator is permitted to market any of our product candidates in the United States until we or they receive regulatory approval of an NDA from the FDA.

In order to obtain approval to commercialize a product candidate in the United States or abroad, we or our collaborators must demonstrate to the satisfaction of the FDA or foreign regulatory agencies, that such product candidates are safe and effective for their intended uses. Results from non-clinical studies and clinical trials can be interpreted in different ways. Even if we believe that the non-clinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA and other regulatory authorities. Although we are conducting our Phase 3 clinical trials pursuant to SPA agreements, the FDA may still require us to conduct additional non-clinical studies or clinical trials for our product candidates either prior to or post-approval, and it may otherwise object to elements of our clinical development program.

We have not submitted an NDA for any of our product candidates. 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 FDA has substantial discretion in the review and approval process and may refuse to accept for filing any application or may decide that our data is insufficient for approval and require additional non-clinical, clinical or other studies. Foreign regulatory authorities have differing requirements for approval of drugs 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 affect our ability to obtain marketing approval in other jurisdictions. The FDA or any foreign regulatory body can delay, limit or deny approval of our product candidates or require us to conduct additional non-clinical or clinical testing or abandon a program for many reasons, including:

- the FDA or the applicable foreign regulatory agency's disagreement with the design or implementation of our clinical trials, although we are conducting our Phase 3 clinical trials pursuant to SPA agreements;
- negative or ambiguous results from our clinical trials or results that may not meet the level of statistical significance required by the FDA or comparable foreign regulatory agencies for approval;
- serious and unexpected drug-related side effects experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates;
- our inability to demonstrate to the satisfaction of the FDA or the applicable foreign regulatory body that our product candidates are safe and effective for the proposed indication(s);
- the FDA's or the applicable foreign regulatory agency's disagreement with the interpretation of data from non-clinical studies or clinical trials;
- our inability to demonstrate the clinical and other benefits of our product candidates outweigh any safety or other perceived risks;
- the FDA's or the applicable foreign regulatory agency's requirement for additional non-clinical studies or clinical trials;
- the FDA's or the applicable foreign regulatory agency's disagreement regarding the formulation, labeling and/or the specifications for our product candidates; or
- the potential for approval policies or regulations of the FDA or the applicable foreign regulatory agencies to significantly change in a manner rendering our clinical data insufficient for approval.

Of the large number of drugs in development, only a small percentage complete the FDA or foreign regulatory approval processes and are successfully commercialized. The lengthy review process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval, which would significantly harm our business, financial condition, results of operations and growth prospects.

Even if we eventually receive approval of an NDA or foreign marketing application for our product candidates, the FDA or the applicable foreign regulatory agency may grant approval contingent on the performance of costly additional clinical trials, often referred to as Phase 4 clinical trials, and the FDA may require the implementation of a REMS, which may be required to ensure safe use of the drug after approval. The FDA or the applicable regulatory agency also may approve a product candidate for a more limited indication or patient population than we originally requested, and the FDA or applicable foreign regulatory agency may not approve the labeling that we believe is necessary or desirable for the successful commercialization of a product candidate. Any delay in obtaining, or inability to obtain, applicable regulatory approval would delay or prevent commercialization of that product candidate and would materially adversely impact our business and prospects.

***Future legislation and/or regulations and policies adopted by the FDA, the EMA or similar regulatory authorities may increase the time and cost required for us to conduct and complete clinical trials of oral sulopenem, sulopenem and other potential product candidates.***

The FDA has established regulations to govern the drug development and approval process, as have foreign regulatory authorities. The policies of the FDA and other regulatory authorities may change and additional laws may be enacted or government regulations may be promulgated that could prevent, limit, delay, or alternatively accelerate regulatory review of our product candidates.

***If we are unable to obtain marketing approval in jurisdictions outside the United States, we will not be able to market our product candidates outside of the United States.***

In order to market and sell oral sulopenem, sulopenem or our other future product candidates in the European Union and many other jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. 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. The approval procedure varies among countries and can involve additional testing. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory 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, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside the United States on a timely basis or at all.

We are currently evaluating our commercialization strategy in the United States and other territories. We believe that in addition to the United States, Europe represents a significant market opportunity because of rising rates of extended spectrum ß-lactamases (ESBL) resistance. On June 23, 2016, the electorate in the United Kingdom (UK) voted in favor of leaving the European Union (EU), commonly referred to as Brexit. On March 29, 2017, the country formally notified the EU of its intention to withdraw from the EU pursuant to Article 50 of the Lisbon Treaty, commencing a period of two years, unless extended, for the UK and other EU member states to negotiate the terms of the withdrawal. There has been limited progress so far in the negotiations and continued uncertainty in the UK government which increases the possibility of the UK exiting the EU on April 12, 2019 without a formal withdrawal agreement in place and of significant market and economic disruption as a result. Brexit could adversely affect European or worldwide political, regulatory, economic or market conditions and could contribute to instability in global political institutions, regulatory agencies and financial markets. Since a significant proportion of the regulatory framework in the UK is derived from EU directives and regulations, Brexit could materially impact the regulatory regime with respect to the approval of our product candidates in the UK or the EU. Any delay in obtaining, or an inability to obtain, any regulatory approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the UK and/or the EU 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 UK and/or EU for our product candidates, which could significantly and materially harm our business.

***Non-U.S. regulatory authorities may require us to conduct additional clinical trials or non-clinical studies to accommodate submission for the cUTI indication.***

We obtained scientific advice from the EMA for each of the Phase 3 clinical trials in the uUTI, cUTI and cIAI indications, as well as to gain alignment on non-clinical supportive information required for EMA submission. We are not in alignment with regard to the comparator agent selected for the cUTI clinical trial and are considering other options to accommodate a European filing for this indication. The EMA may request that we conduct one or more additional clinical trials or non-clinical studies to support potential approval for oral sulopenem and sulopenem for the cUTI indication. We cannot predict how the EMA will interpret the data and results from our Phase 3 clinical trial and other elements of our development program, or whether oral sulopenem or sulopenem will receive any regulatory approvals in the EU.

***If we receive regulatory approval for any product candidate we will be subject to ongoing obligations and continuing regulatory review, which may result in significant additional expense. Our product candidates, including oral sulopenem and sulopenem, if approved, 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 our product candidates, when and if approved.***

Any product candidate, including oral sulopenem and sulopenem, for which we obtain marketing approval will also be subject to ongoing regulatory requirements for labeling, packaging, storage, distribution, advertising, promotion, record-keeping and submission of safety and other postmarketing information. For example, approved products, manufacturers and manufacturers' facilities are required to comply with extensive FDA requirements, 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 will also be required to report certain adverse reactions and production problems, if any, to the FDA 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 may also require a REMS as a condition of approval of our product candidates, which could include requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure that drugs are marketed only for the approved indications and in accordance with the provisions of the approved labelling and regulatory requirements. The FDA also imposes stringent restrictions on manufacturers' communications regarding off-label use 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 marketing.

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 fines, warning letters, untitled letters or impose holds on clinical trials if any are still ongoing;
- mandate modifications to promotional materials or require provision of corrective information to healthcare practitioners;
- impose restrictions on the product or its manufacturers or 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 non-compliance;
- suspend or withdraw marketing approvals;
- refuse to permit the import or export of the product;
- seize or detain supplies of the product; or
- issue injunctions or impose civil or criminal penalties.

***If we fail to comply with federal and state healthcare laws, including fraud and abuse and health information privacy and security laws, we could face substantial penalties and our business, results of operations, financial condition and prospects could be adversely affected.***

As a pharmaceutical company, even though we do not provide healthcare services or receive payments directly from or bill directly to Medicare, Medicaid or other third-party payors for our products, certain federal and state healthcare laws and regulations pertaining to fraud and abuse, patients' rights and other healthcare laws and regulations, are applicable to our business. We are subject to healthcare laws and regulations by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute which prohibits, among other things, any person or entity, from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for either the referral of an individual, or the purchase, lease, furnishing, prescribing, ordering or recommendation of an item, good, facility or service reimbursable by a federally funded healthcare program, such as the Medicare or Medicaid program. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers and formulary managers on the other hand. The term "remuneration" has been interpreted broadly and may constrain our marketing practices, educational programs, pricing policies and relationships with healthcare providers or other entities, among other activities;

- the federal civil and criminal false claims laws, including the federal False Claims Act, and false statement laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid or other government payors that are false or fraudulent or making any materially false statement in connection with the delivery or payment for healthcare benefits, items or services. Pharmaceutical manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims;
- the Health Insurance Portability and Accountability Act of 1996 (HIPAA), which, among other things, imposes criminal liability for executing or attempting to execute a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and creates federal criminal laws that prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statements or representations, 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, benefits, items or services;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH) and their respective implementing regulations, including the final omnibus rule published on January 25, 2013, mandates, among other things, the adoption of uniform standards for the electronic exchange of information in common healthcare transactions, as well as standards relating to the privacy, security, transmission and breach reporting of individually identifiable health information, upon certain health plans, healthcare clearinghouses and healthcare providers and their respective business associates that perform services for them involving individually identifiable health information, which require the adoption of administrative, physical and technical safeguards to protect such information. Among other things, HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in U.S. federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions;
- the federal physician payment transparency requirements, sometimes referred to as the "Physician Payments Sunshine Act," and its implementing regulations, which imposes annual disclosure requirements to the Centers for Medicare and Medicaid Services (CMS) on certain manufacturers of drugs, biologics, devices and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions), of certain payments or other transfers of value made to physicians and teaching hospitals, as well as ownership or investment interests held by physicians and their immediate family members;
- state and foreign law equivalents of each of the above federal laws, such as anti-kickback and false claims laws, which may apply to items or services reimbursed by any third-party payor, including commercial insurers, which may impose similar or more prohibitive restrictions;
- state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts;
- state, local and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, obtain pharmaceutical agent licensure, and/or otherwise restrict payments that may be made to healthcare providers and entities;
- state and local laws that require the registration of pharmaceutical sales representatives; and
- state, local and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to other healthcare providers or entities or marketing expenditures.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Additionally, the Patient Protection and Affordable Care Act (as amended by the Health Care and Education Reconciliation Act), enacted in 2010 (ACA), among other things, amended the intent requirement of the federal Anti-Kickback Statute and criminal health care fraud statutes, so that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. In addition, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitute a false or fraudulent claim for purposes of the False Claims Act.

Recently, several pharmaceutical and other healthcare companies have been prosecuted under the federal false claims laws for allegedly inflating drug prices they report to pricing services, which in turn are used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. To the extent that any product we make is sold in a country outside of the United States, we may be subject to similar laws and regulations.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional congressional action is taken. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used.

Since enactment of the ACA, there have been numerous legal challenges and congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate". The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Further, each chamber of the Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. The Congress will likely consider other legislation to replace elements of the ACA, during the next congressional session. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provision. We will continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business.

The Trump administration has also taken executive actions to undermine or delay implementation of the ACA. Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

The costs of prescription pharmaceuticals has also been the subject of considerable discussion in the United States, and members of Congress and the Administration have stated that they will address such costs through new legislative and administrative measures. To date, there have been several recent U.S. congressional inquiries and proposed and enacted state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, 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. 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.

Specifically, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on May 11, 2018, the Trump administration issued a plan to lower drug prices. Under this blueprint for action, the Trump administration indicated that HHS will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. More recently, on January 31, 2019, the HHS Office of Inspector General proposed modifications to the federal Anti-Kickback Statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations.

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.

The risks of complying with these laws cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security, fraud and transparency laws is time consuming and costly. If our past or present operations, or those of our distributors are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to sanctions, including civil, criminal and administrative penalties, fines, damages, disgorgement, exclusion from participation in U.S. federal or state health care programs, individual imprisonment, additional reporting obligations and oversight if subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could materially adversely affect our ability to operate our business and our financial results. Similarly, if healthcare providers, distributors or other entities with whom we do business are found to be out of compliance with applicable laws and regulations, they may be subject to sanctions, which could also have a negative impact on us.

***We are subject to various laws protecting the confidentiality of certain patient health information, and our failure to comply could result in penalties and reputational damage.***

Certain countries in which we operate have, or are developing, laws protecting the confidentiality of certain patient health information. EU member states and other jurisdictions have adopted data protection laws and regulations, which impose significant compliance obligations.

For example, the EU General Data Protection Regulation became enforceable on May 25, 2018 replacing the EU Data Protection Directive. In addition to imposing strict obligations and restrictions on the ability to collect, analyze and transfer personal data, including health data from clinical trials and adverse event reporting (as previously applied under the EU Data Protection Directive), the EU General Data Protection Regulation introduced new data protection requirements in the EU and substantial fines for breaches of the data protection rules. It also increased our responsibility and liability in relation to personal data that we process and requires us to put in place additional mechanisms to ensure compliance with the new EU data protection rules.

The EU General Data Protection Regulation permits EU member states to introduce their own local laws to give further effect to the EU General Data Protection Regulation locally and permits local derogations to certain provisions, adding to the complexity of processing personal data in the EU. As the EU General Data Protection Regulation has only recently come into force, there is limited guidance available on implementation and compliance practices.

The EU General Data Protection Regulation prohibits the transfer of personal data to countries outside of the EU member states that are not considered by the European Commission to provide an adequate level of data protection, and transfers of personal data to such countries can only be made in certain circumstances—for example, where the transfer is required by law or the data subject (i.e. the individual to whom the personal data relates) has given his or her consent to the transfer. We have policies and practices that we believe make us compliant with applicable privacy regulations and are continuously updating these to ensure compliance with the new EU General Data Protection Regulation and associated guidance on implementation and compliance practices. Nevertheless, any failure to comply with the rules arising from the EU General Data Protection Regulation and national laws of EU member states, as well as privacy laws in other countries in which we operate, could lead to government enforcement actions and significant sanctions or penalties against us, adversely impact our results of operations and subject us to negative publicity.

***Healthcare legislative reform measures may have a material adverse effect on our business and results of operations***

In the United States, there have been and continue to be a number of legislative and regulatory changes, and proposed changes, that could affect the future results of our business and operations. In particular, there have been and continue to be a number of initiatives at the federal and states levels that seek to reduce healthcare costs. For example, in March 2010 the ACA was enacted, which has substantially changed the way health care is financed by both governmental and private insurers, and significantly impacted the U.S. pharmaceutical industry. Among the provisions of the ACA, of greatest importance to the pharmaceutical and biotechnology industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively, and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price (AMP);
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics that are inhaled, infused, instilled, implanted or injected;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (and 70% commencing January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- expansion of the entities eligible for discounts under the Public Health program;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- establishment of a Center for Medicare Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending; and
- implementation of the federal physician payment transparency requirements, sometimes referred to as the "Physician Payments Sunshine Act."

Some of the provisions of the ACA have yet to be fully implemented, and there have been legal and political challenges to certain aspects of the ACA. Since January 2017, President Trump has signed two executive orders and other directives designed to delay, circumvent, or loosen certain requirements mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the 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, that is commonly referred to as the "individual mandate." Additionallyon January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, 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 (BBA), among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". More recently, in July 2018, CMS published a final rule permitting further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. We continue to evaluate how the ACA and recent efforts to repeal and replace or limit the implementation of the ACA will impact our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2 percent per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2027 unless additional Congressional action is taken. Moreover, in January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Further, there has been heightened governmental scrutiny in the United States of the manner in which manufacturers set prices for their marketed products in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. At the federal level, 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 c ost 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. HHS has already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. Although a number of these, and other potential proposals, will require authorization through additional legislation to become effective, C ongress 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 have increasingly passed legislation and implemented 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. These new laws and initiatives may result in additional reductions in Medicare and other healthcare funding, as well as 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, all of which could have a material adverse effect on our future customers and accordingly, our financial operations.

Additionally, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017 (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.

***Our employees, independent contractors, principal investigators, CROs, consultants or vendors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements.***

We are exposed to the risk that our employees, independent contractors, principal investigators, CROs, consultants or vendors may engage in fraudulent or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: FDA regulations, including those laws requiring the reporting of true, complete and accurate information to the FDA; manufacturing standards; federal and state healthcare fraud and abuse laws and regulations; or laws that require the true, complete and accurate reporting of financial information or data. Specifically, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent

fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of clinical trials or creating fraudulent data in our preclinical studies or clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct by our employees and other third parties, 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 or regulations. Additionally, we are subject to the risk that a person could allege such fraud or other misconduct, even if none occurred. 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, including the imposition of civil, criminal and administrative penalties, damages, monetary fines, disgorgement, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, individual imprisonment, additional reporting obligations and oversight if subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, curtailment of our operations, contractual damages, reputational harm, and diminished potential profits and future earnings, any of which could adversely affect our business, financial condition, results of operations orgrowth prospects.

**Risks Related to Employee Matters and Managing Growth**

***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 development, regulatory, commercialization and business development expertise of Corey N. Fishman, our Chief Executive Officer, and Michael W. Dunne, M.D., our Chief Scientific Officer, 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. We do not maintain “key man” insurance with respect to any of our executive officers or key 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 product candidates 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 engaged by entities 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.

***We expect to grow our organization, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.***

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development, manufacturing, regulatory affairs, sales, marketing and health resources. Our management may need to divert a disproportionate amount of its attention away from our day-to-day activities to devote time to managing these growth activities. To manage these growth activities, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. Our inability to effectively manage the expansion of our operations may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If our management is unable to effectively manage our expected growth, our expenses may increase more than expected, our potential ability to generate revenue could be reduced and we may not be able to implement our business strategy.

***If approvals are obtained outside of the United States, we will be subject to additional risks in conducting business in those markets.***

Even if we are able to obtain approval for commercialization of a product candidate in a country outside of the United States, we will be subject to additional risks related to international business operations, 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 market outside of the United States (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 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.

These and other risks may materially adversely affect our ability to attain or sustain revenue from markets outside of the United States.

***We may engage in acquisitions that could disrupt our business, cause dilution to our shareholders or reduce our financial resources.***

In the future, we may enter into transactions to acquire other businesses, products or technologies. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our ordinary shares or other equity securities to the shareholders of the acquired company, which would reduce the percentage ownership of our then current shareholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and nondisruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results.

**Risks Related to Taxation**

***We believe we may have been a passive foreign investment company for U.S. federal income tax purposes in the past and we could be a passive foreign investment company in the future, which could subject U.S. Holders to adverse U.S. federal income tax consequences.***

Based on our gross income and average value of our gross assets, we do not believe we (or our wholly-owned, non-U.S. subsidiary) were a passive foreign investment company (PFIC) for the tax year ended December 31, 2018. Our status, and the status of our non-U.S. subsidiary, in any taxable year will depend on our assets and activities in each year, and because this is a factual determination made annually after the end of each taxable year, there can be no assurances as to our PFIC status for the current taxable year or any future taxable year. We believe that we, including our non-U.S. subsidiary, may have been a PFIC for our taxable years ended December 31, 2017 and 2016.

We will be a PFIC in any taxable year if at least (i) 75% of our gross income is "passive income" or (ii) 50% of the average gross value of our assets, determined on a quarterly basis, is attributable to assets that produce, or are held for the production of, passive income. We refer to the passive income test as the "PFIC Income Test" and the asset test as the "PFIC Asset Test".

As used in this section, *Risks Related to Taxation*, the term "U.S. Holder" means a beneficial owner of our ordinary shares that is, for U.S. federal income tax purposes, (1) an individual who is a citizen or resident of the United States, (2) a corporation (or entity treated as a corporation for U.S. federal income tax purposes) created or organized in or under the laws of the United States, any state thereof, or the District of Columbia, (3) an estate the income of which is subject to U.S. federal income tax regardless of its 168 source

or (4) a trust (x) with respect to which a court within the United States is able to exercise primary supervision over its administration and one or more United States persons have the authority to control all of its substantial decisions or (y) that has elected under applicable U.S. Treasury regulations to be treated as a domestic trust for U.S. federal income tax purposes.

If we are a PFIC in any taxable year in which a U.S. Holder holds shares, subject to the next sentence, we always will be a PFIC with respect to those shares, regardless of the results of the PFIC Income Test or the PFIC Asset Test as applied to us in subsequent years. However, under applicable Treasury regulations, if the preceding sentence applies to a U.S. Holder we will cease to be treated as a PFIC with respect to that U.S. Holder if, in the manner and at the time required by those regulations, the U.S. Holder elects to recognize (and pay tax on, in the manner described in the next paragraph) any unrealized gain in the shares of our stock owned by that U.S. Holder.

If we are a PFIC and a U.S. Holder does not make a mark-to-market election (discussed below) with respect to our ordinary shares, that U.S. Holder may be subject to adverse tax consequences, including deferred tax and interest charges, with respect to certain distributions on our ordinary shares, any gain realized on a disposition of our ordinary shares and certain other events. The effect of these adverse tax consequences could be materially adverse to the shareholder. If, in any taxable year during which a U.S. Holder holds our ordinary shares and our non-U.S subsidiary is a PFIC (i.e., a lower-tier PFIC), such U.S. Holder would be treated as owning a proportionate amount (by value) of the shares of the lower-tier PFIC and would be taxed under the PFIC excess distribution regime on distributions by the lower-tier PFIC and on gain from the disposition of shares of the lower-tier PFIC even though such U.S. Holder would not receive the proceeds of those distributions or dispositions.

If a U.S. Holder makes a valid, timely mark-to-market election with respect to our ordinary shares, that U.S. Holder will recognize as ordinary income or loss in each year that we meet the PFIC Income Test or PFIC Asset Test an amount equal to the difference between that U.S. Holder's adjusted basis in our ordinary shares and the fair market value of the ordinary shares, thus also possibly giving rise to phantom income and a potential out-of-pocket tax liability. Ordinary loss generally is recognized only to the extent of net mark-to-market gains previously included in income. U.S. Holders should also be aware that the mark-to-market election generally will not be available with respect to any of our subsidiaries that is a PFIC and that gain recognized on the sale of our ordinary shares that is attributable to a subsidiary that is a PFIC may result in such gain being subject to deferred tax and interest charges.

We currently intend to make available the information necessary to permit a U.S. Holder to make a qualified electing fund, or "QEF election," under the U.S. federal income tax laws, which may mitigate some of the adverse U.S. federal income tax consequences that could apply to a U.S. Holder. However, we may choose not to provide such information at a future date.

***If the IRS determines that we are not a PFIC, and a U.S. Holder previously paid taxes pursuant to a mark-to-market election, they may have paid more taxes than they legally owed.***

If the U.S. Internal Revenue Service (IRS) makes a determination that we were not a PFIC in a prior taxable year and a U.S. Holder previously paid taxes pursuant to a mark-to-market election, that U.S. Holder may have paid more taxes than were legally owed due to such election. If such U.S. Holder does not, or is not able to, file a refund claim before the expiration of the applicable statute of limitations, that U.S. Holder will not be able to claim a refund for those taxes.

***Changes to U.S. federal income tax laws could have material consequences for us and U.S. Holders of our ordinary shares.***

Future U.S. legislation, U.S. Treasury regulations and IRS rulings could affect the U.S. federal income tax treatment of us and U.S. Holders of our ordinary shares.

***A future transfer of a shareholder's ordinary shares, other than one effected by means of the transfer of book entry interests in DTC, may be subject to Irish stamp duty.***

Transfers of our ordinary shares effected by means of the transfer of book entry interests in the Depository Trust Company (DTC) should not be subject to Irish stamp duty. Where the ordinary shares are traded through DTC through brokers who hold such ordinary shares on behalf of customers an exemption should be available because our ordinary shares are traded on a recognized stock exchange in the U.S. However, if a shareholder holds their ordinary shares directly rather than beneficially through DTC through a broker, any transfer of their ordinary shares could be subject to Irish stamp duty (currently at the rate of 1% of the higher of the price paid or the market value of the shares acquired). Payment of Irish stamp duty is generally a legal obligation of the transferee. The potential for stamp duty to arise could adversely affect the price of our ordinary shares.

***Dividends paid by us may be subject to Irish dividend withholding tax.***

We have never declared or paid cash dividends on our ordinary shares and we do not expect to pay dividends for the foreseeable future. To the extent that we do make dividend payments (or other returns to shareholders that are treated as "distributions" for Irish tax purposes), it should be noted that, in certain limited circumstances, dividend withholding tax (currently at a rate of 20%) may arise in respect of dividends paid on our ordinary shares. A number of exemptions from dividend withholding tax exist, such that shareholders resident in EU member states (other than Ireland) or other countries with which Ireland has signed a double tax treaty, which includes the United States, should generally be entitled to exemptions from dividend withholding tax provided that the appropriate documentation is in place. The ability of a U.S. Holder to credit any Irish dividend withholding tax against that U.S. Holder's tentative U.S. federal tax liability may be subject to limitations.

***Dividends received by Irish residents and certain other shareholders may be subject to Irish income tax.***

We have never declared or paid cash dividends on our ordinary shares and we do not expect to pay dividends for the foreseeable future. To the extent that we do make dividend payments (or other returns to shareholders that are treated as "distributions" for Irish tax purposes), it should be noted that shareholders who are entitled to an exemption from Irish dividend withholding tax on dividends received from us will not be subject to Irish income tax in respect of those dividends, unless they have some connection with Ireland other than their shareholding in Iterum Therapeutics plc (for example, they are resident in Ireland) or they hold their ordinary shares through a branch or agency in Ireland which carries out a trade of their behalf. Shareholders who are not resident nor ordinarily resident in Ireland, but who are not entitled to an exemption from Irish dividend withholding tax, will generally have no further liability to Irish income tax on those dividends which suffer dividend withholding tax.

***Our ordinary shares received by means of a gift or inheritance could be subject to Irish capital acquisitions tax.***

Irish capital acquisitions tax (CAT) could apply to a gift or inheritance of our ordinary shares irrespective of the place of residence, ordinary residence or domicile of the parties. This is because our ordinary shares will be regarded as property situated in Ireland. The person who receives the gift or inheritance has primary liability for CAT.

**Risks Related to Our Ordinary Shares**

***An active trading market for our ordinary shares may not be sustained.***

Our ordinary shares began trading on the Nasdaq Global Market on May 25, 2018. Given the limited trading history of our ordinary shares, there is a risk that an active trading market for our shares may not be sustained, which could put downward pressure on the market price of our ordinary shares and thereby affect the ability of shareholders to sell their shares. An inactive trading market for our ordinary shares may also impair our ability to raise capital to continue to fund our operations by issuing shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

***The price of our ordinary shares has been volatile and could be subject to volatility related or unrelated to our operations and our shareholders' investment in us could suffer a decline in value.***

Since our IPO in May 2018, the trading price of our ordinary shares has fluctuated between a low of $5.01 and a high of $13.00 per share. The trading price of our ordinary shares could be subject to wide fluctuations in response to various factors, some of which are beyond our control. These factors include those discussed elsewhere in this "Risk Factors" section of this document and others, such as:

- results from, and any delays in, our current and future clinical trials, in particular our three ongoing Phase 3 clinical trials related to oral sulopenem and sulopenem;
- announcements of regulatory approval or disapproval of oral sulopenem and sulopenem or future product candidates;
- delays in the commercialization of oral sulopenem and sulopenem or any future product candidates;
- manufacturing and supply issues related to our development programs and commercialization of oral sulopenem and sulopenem or any of our future product candidates;
- quarterly variations in our results of operations or those of our competitors;
- changes in our earnings estimates or recommendations by securities analysts;
- announcements by us or our competitors of new product candidates, significant contracts, commercial relationships, acquisitions or capital commitments;
- announcements relating to future development or license agreements including termination of such agreements;

- adverse developments with respect to our intellectual property rights or those of our principal collaborators;
- commencement of litigation involving us or our competitors;
- changes in our board of directors or management;
- new legislation in the United States relating to the prescription, sale, distribution or pricing of drugs;
- product liability claims, other litigation or public concern about the safety of oral sulopenem or sulopenem or future products;
- market conditions in the healthcare market in general, or in the antibiotics segment in particular, including performance of our competitors; and
- general economic conditions in the United States and abroad.

In addition, the stock market in general, or the market for equity securities in our industry or industries related to our industry, may experience extreme volatility unrelated to our operating performance. These broad market fluctuations may adversely affect the trading price or liquidity of our ordinary shares. Any sudden decline in the market price of our ordinary shares could trigger securities class-action lawsuits against us. If any of our shareholders were to bring such a lawsuit against us, we could incur substantial costs defending the lawsuit and the time and attention of our management would be diverted from our business and operations. We also could be subject to damages claims if we are found to be at fault in connection with a decline in our share price.

***If securities or industry analysts do not publish research or reports about our company, or if they issue adverse or misleading opinions regarding us or our ordinary shares, our share price and trading volume could decline.***

The trading market for our ordinary shares relies, in part, on the research and reports that industry or financial analysts publish about our company. If no, or only a few, analysts publish research or reports about our company, the market price for our ordinary shares may be adversely affected. Our share price also may decline if any analyst who covers us issues an adverse or misleading opinion regarding us, our business model, our intellectual property or our share performance, or if our pivotal safety and efficacy studies and operating results fail to meet analysts' expectations. If one or more analysts cease coverage of us 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 and possibly adversely affect our ability to engage in future financings.

***Our principal shareholders and management own a significant percentage of our ordinary shares and will be able to exert significant control over matters subject to shareholder approval.***

Based on shares outstanding as of February 28, 2019, our executive officers, directors, holders of 5% or more of our ordinary shares and their respective affiliates beneficially own in the aggregate approximately 68.6% of our outstanding ordinary shares. As a result of their share ownership, these holders may have the ability to influence our management and policies and will be able to significantly affect the outcome of matters requiring shareholder approval such as elections of directors, amendments of our organizational documents or approvals of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our ordinary shares that our shareholders may feel are in their best interest.

***If we raise additional capital in the future, our existing shareholders' level of ownership in our Company could be diluted or require us to relinquish rights.***

Any issuance of securities we may undertake in the future to raise additional capital could cause the price of our ordinary shares to decline, or require us to issue shares at a price that is lower than that paid by holders of our ordinary shares in the past, which would result in those newly issued shares being dilutive.

Further, if we obtain funds through a debt financing or through the issuance of debt or preference securities, these securities would likely have rights senior to the rights of our ordinary shareholder, which could impair the value of our ordinary shares. Any debt financing we enter into may include covenants that limit our flexibility in conducting our business. We also could be required to seek funds through arrangements with collaborators or others, which might require us to relinquish valuable rights to our intellectual property or product candidates that we would have otherwise retained.

***Sales of a substantial number of our ordinary shares in the public market, or the perception that these sales could occur, could cause our share price to fall.***

A portion of our outstanding ordinary shares can be traded without restriction at any time. A substantial portion of our outstanding ordinary shares is currently restricted as a result of federal securities laws but can be sold at any time subject to applicable volume limitations. In addition, a portion of our ordinary shares is currently restricted as a result of contractual provisions

until November 2019. As such, sales of a substantial number of our ordinary shares in the public market could occur at any time If our current shareholders sell, or indicate an intention to sell, substantial amounts of our ordinary shares in the public market, the trading price of our ordinary shares could decline.

In addition, ordinary shares that are issuable upon exercise of outstanding options, or reserved for future issuance under our equity incentive plans or issuable upon exercise of outstanding warrants will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act. If these additional ordinary shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our ordinary shares could decline.

***Irish law differs from the laws in effect in the United States and may afford less protection to holders of our securities.***

Shareholders may have difficulties enforcing, in actions brought in courts in jurisdictions located outside the United States, judgments obtained in the U.S. courts under the U.S. securities laws. In particular, if a shareholder sought to bring proceedings in Ireland based on U.S. securities laws, the Irish court might consider:

- that it did not have jurisdiction;
- that it was not the appropriate forum for such proceedings;
- that, applying Irish conflict of law rules, U.S. law (including U.S. securities laws) did not apply to the relationship between the shareholder and us or our directors and officers; or
- that the U.S. securities laws were of a penal nature and violated Irish public policy and should not be enforced by the Irish court.

It may not be possible to enforce court judgments obtained in the United States against us in Ireland based on the civil liability provisions of the U.S. federal or state securities laws. In addition, there is some uncertainty as to whether the courts of Ireland would recognize or enforce judgments of U.S. courts obtained against us or our directors or officers based on the civil liabilities provisions of the U.S. federal or state securities laws. We have been advised that the United States currently does not have a treaty with Ireland providing for the reciprocal recognition and enforcement of judgments in civil and commercial matters. Therefore, a final judgment for the payment of money rendered by any U.S. federal or state court based on civil liability, whether or not based solely on U.S. federal or state securities laws, would not automatically be enforceable in Ireland.

A judgment obtained against us will be enforced by the courts of Ireland only if the following general requirements are met:

- U.S. courts must have had jurisdiction in relation to the particular defendant according to Irish conflict of law rules (the submission to jurisdiction by the defendant would satisfy this rule); and
- the judgment must be final and conclusive and the decree must be final and unalterable in the court which pronounces it.

A judgment can be final and conclusive even if it is subject to appeal or even if an appeal is pending. But where the effect of lodging an appeal under the applicable law is to stay execution of the judgment, it is possible that in the meantime the judgment may not be actionable in Ireland. It remains to be determined whether final judgment given in default of appearance is final and conclusive. Irish courts may also refuse to enforce a judgment of the U.S. courts which meets the above requirements for one of the following reasons:

- the judgment is not for a definite sum of money;
- the judgment was obtained by fraud;
- the enforcement of the judgment in Ireland would be contrary to natural or constitutional justice;
- the judgment is contrary to Irish public policy or involves certain U.S. laws which will not be enforced in Ireland; or
- jurisdiction cannot be obtained by the Irish courts over the judgment debtors in the enforcement proceedings by personal service in Ireland or outside Ireland under Order 11 of the Irish Superior Courts Rules.

As an Irish company, we are governed by the Irish Companies Act 2014 (the Irish Companies Act), which differs in some material respects from laws generally applicable to U.S. corporations and shareholders, including, among others, differences relating to interested director and officer transactions and shareholder lawsuits. Likewise, the duties of directors and officers of an Irish company generally are owed to the company only. Shareholders of Irish companies generally do not have a personal right of action against directors or officers of the company and may exercise such rights of action on behalf of the company only in limited circumstances. Accordingly, holders of our securities may have more difficulty protecting their interests than would holders of securities of a corporation incorporated in a jurisdiction of the United States.

Our shareholders should also be aware that Irish law does not allow for any form of legal proceedings directly equivalent to the class action available in the United States.

***As a newly public company, we have incurred and will incur significant additional costs, and our management is required to devote substantial time and attention to our public reporting obligations.***

As a publicly-traded company, we have incurred and will incur significant additional legal, accounting and other expenses compared to historical levels. In addition, new and changing laws, regulations and standards relating to corporate governance and public disclosure, including the Dodd-Frank Wall Street Reform and Consumer Protection Act and the rules and regulations promulgated and to be promulgated thereunder, as well as under the Sarbanes-Oxley Act of 2002 (the Sarbanes-Oxley Act), the JOBS Act and the rules and regulations of the U.S. Securities and Exchange Commission (the SEC), and the Nasdaq Global Market, have created uncertainty for public companies and increased our costs and time that our board of directors and management must devote to complying with these rules and regulations. We expect these rules and regulations to increase our legal and financial compliance costs substantially and lead to diversion of management time and attention from revenue-generating activities.

***We are an "emerging growth company," and the reduced disclosure requirements applicable to "emerging growth companies" may make our ordinary shares less attractive to investors.***

We are an "emerging growth company" as defined in the JOBS Act, and, therefore, we may take advantage of reduced disclosure and regulatory requirements that are otherwise generally applicable to public companies, including not being required to have our internal control over financial reporting audited by our independent registered public accounting firm pursuant to Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and any golden parachute payments. We may take advantage of these reduced disclosure and regulatory requirements until we are no longer an "emerging growth company." We may remain an "emerging growth company" until as late as December 31, 2023 (the fiscal year-end following the fifth anniversary of our IPO), although we may cease to be an "emerging growth company" earlier under certain circumstances, including if the market value of our ordinary shares that is held by non-affiliates exceeds $700 million as of any June 30, in which case we would cease to be an "emerging growth company" as of the following December 31, or if our gross revenue exceeds $1.07 billion in any fiscal year. In addition, the JOBS Act provides that an emerging growth company can delay adopting new or revised accounting standards until those standards apply to private companies. We have irrevocably elected not to avail ourselves of this delayed adoption of new or revised accounting standards and, therefore, we are subject to the same new or revised accounting standards as public companies that are not emerging growth companies.

The exact implications of the JOBS Act are still subject to interpretations and guidance by the SEC and other regulatory agencies, and we may not be able to take advantage of all of the benefits of the JOBS Act. In addition, investors may find our ordinary shares less attractive if we rely on the exemptions and relief granted by the JOBS Act. If some investors find our ordinary shares less attractive as a result, there may be a less active trading market for our ordinary shares and our share price may decline or become more volatile.

***If we fail to maintain an effective system of disclosure controls and internal control over financial reporting, our ability to produce timely and accurate financial statements or comply with applicable regulations could be impaired.***

As a public company, we are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, the Sarbanes-Oxley Act, and the rules and regulations of the applicable listing standards of the Nasdaq Global Market. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting. Our current controls and any new controls that we develop may become inadequate because of changes in conditions in our business. Further, weaknesses in our disclosure controls and internal control over financial reporting may be discovered in the future. Any failure to develop or maintain effective controls or any difficulties encountered in their implementation or improvement could harm our results of operations or cause us to fail to meet our reporting obligations and may result in a restatement of our consolidated financial statements for prior periods. Any failure to implement and maintain effective internal control over financial reporting could also adversely affect the results of periodic management evaluations and annual independent registered public accounting firm attestation reports regarding the effectiveness of our internal control over financial reporting that we will eventually be required to include in our periodic reports that will be filed with the SEC. Ineffective disclosure controls and procedures and internal control over financial reporting could also cause investors to lose confidence in our reported financial and other information, which would likely have a negative effect on the trading price of our ordinary shares. In addition, if we are unable to continue to meet these requirements, we may not be able to remain listed on the Nasdaq Global Market.

Pursuant to Section 404 of the Sarbanes-Oxley Act, we are required to furnish a report by our management on our internal control over financial reporting beginning with our second filing of an Annual Report on Form 10-K with the SEC after we become a public company. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with

Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps 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. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, 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.

Any failure to maintain effective disclosure controls and internal control over financial reporting could have a material and adverse effect on our business, results of operations and financial condition and could cause a decline in the trading price of our ordinary shares.

***We have never paid cash dividends, do not anticipate paying any cash dividends and our ability to pay dividends, or repurchase or redeem our ordinary shares, is limited by law.***

We have never declared or paid cash dividends on our ordinary shares and do not anticipate paying any dividends on our ordinary shares in the foreseeable future. Any determination to pay dividends in the future will be at the sole discretion of our board of directors after considering our financial condition, results of operations, capital requirements, contractual restrictions, general business conditions and other factors our board of directors deems relevant, and subject to compliance with applicable laws, including the Irish Companies Act which requires Irish companies to have distributable reserves available for distribution equal to or greater than the amount of the proposed dividend. Distributable reserves are the accumulated realized profits of the company that have not previously been utilized in a distribution or capitalization less accumulated realized losses that have not previously been written off in a reduction or reorganization of capital. Unless the company creates sufficient distributable reserves from its business activities, the creation of such distributable reserves would involve a reduction of the company's share premium account, which would require the approval of (i) 75% of our shareholders present and voting at a shareholder meeting, and (ii) the Irish High Court. In the event that we do not undertake a reduction of capital to create distributable reserves, no distributions by way of dividends, share repurchases or otherwise will be permitted under Irish law until such time as the company has created sufficient distributable reserves from its business activities. In addition, our ability to pay cash dividends is currently prohibited by the terms of our credit facility with SVB.

Accordingly, the only opportunity for a shareholder to achieve a return on their investment in our company is expected to be if the market price of our ordinary shares appreciates and they sell their ordinary shares at a profit.

***Anti-takeover provisions in our Articles of Association and under Irish law could make an acquisition of us more difficult, limit attempts by our shareholders to replace or remove our current directors and management team, and limit the market price of our ordinary shares.***

Our Articles contain provisions that may delay or prevent a change of control, discourage bids at a premium over the market price of our ordinary shares, and adversely affect the market price of our ordinary shares and the voting and other rights of the holders of our ordinary shares. These provisions include:

- dividing our board of directors into three classes, with each class serving a staggered three-year term;
- permitting our board of directors to adopt a shareholder rights plan upon such terms and conditions as it deems expedient and in our best interests;
- permitting our board of directors to issue additional preference shares, with such rights, preferences and privileges as they may designate;
- establishing an advance notice procedure for shareholder proposals to be brought before an annual meeting, including proposed nominations of persons for election to our board of directors; and
- imposing particular approval and other requirements in relation to certain business combinations.

These provisions would apply even if the offer may be considered beneficial by some shareholders. In addition, these provisions may frustrate or prevent any attempts by our shareholders to replace or remove our current management team by making it more difficult for shareholders to replace members of our board of directors, which is responsible for appointing the members of our management.

***Irish law differs from the laws in effect in the United States with respect to defending unwanted takeover proposals and may give our board of directors less ability to control negotiations with hostile offerors.***

Following the authorization for trading of our ordinary shares on the Nasdaq Global Market, we became subject to the Irish Takeover Panel Act, 1997, Irish Takeover Rules 2013 (Irish Takeover Rules). Under the Irish Takeover Rules, our board of directors is

not permitted to take any action that might frustrate an offer for our ordinary shares once our board of directors has received an approach that may lead to an offer or has reason to believe that such an offer is or may be imminent, subject to certain exceptions. Potentially frustrating actions such as (i) the issue of shares, options, restricted share units or convertible securities, (ii) material acquisitions or disposals, (iii) entering into contracts other than in the ordinary course of business or (iv) any action, other than seeking alternative offers, which may result in frustration of an offer, are prohibited during the course of an offer or at any earlier time during which our board of directors has reason to believe an offer is or may be imminent. These provisions may give our board of directors less ability to control negotiations with hostile offerors than would be the case for a corporation incorporated in a jurisdiction of the United States.

***The operation of the Irish Takeover Rules may affect the ability of certain parties to acquire our ordinary shares.***

Under the Irish Takeover Rules, if an acquisition of ordinary shares were to increase the aggregate holding of the acquirer and its concert parties to ordinary shares that represent 30% or more of the voting rights of the company, the acquirer and, in certain circumstances, its concert parties would be required (except with the consent of the Irish Takeover Panel) to make an offer for the outstanding ordinary shares at a price not less than the highest price paid for the ordinary shares by the acquirer or its concert parties during the previous 12 months. This requirement would also be triggered by an acquisition of ordinary shares by a person holding (together with its concert parties) ordinary shares that represent between 30% and 50% of the voting rights in the company if the effect of such acquisition were to increase that person's percentage of the voting rights by 0.05% within a 12 month period. Under the Irish Takeover Rules, certain separate concert parties are presumed to be acting in concert. Our board of directors and their relevant family members, related trusts and "controlled companies" are presumed to be acting in concert with any corporate shareholder who holds 20% or more of our shares. The application of these presumptions may result in restrictions upon the ability of any of the concert parties and/or members of our board of directors to acquire more of our securities, including under the terms of any executive incentive arrangements. In the future, we may consult with the Irish Takeover Panel with respect to the application of this presumption and the restrictions on the ability to acquire further securities, although we are unable to provide any assurance as to whether the Irish Takeover Panel will overrule this presumption. Accordingly, the application of the Irish Takeover Rules may restrict the ability of certain of our shareholders and directors to acquire our ordinary shares.

***As an Irish public limited company, certain capital structure decisions require shareholder approval, which may limit our flexibility to manage our capital structure.***

Under Irish law, our authorized share capital can be increased by an ordinary resolution of our shareholders and the directors may issue new ordinary or preferred shares up to a maximum amount equal to the authorized but unissued share capital, without shareholder approval, once authorized to do so by our Articles of Association or by an ordinary resolution of our shareholders. Additionally, subject to specified exceptions, Irish law grants statutory preemption rights to existing shareholders where shares are being issued for cash consideration but allows shareholders to disapply such statutory preemption rights either in our Articles of Association or by way of special resolution. Such disapplication can either be generally applicable or be in respect of a particular allotment of shares. Accordingly, our Articles of Association contains, as permitted by Irish company law, provisions authorizing the board to issue new shares, and to disapply statutory preemption rights. The authorization of the directors to issue shares and the disapplication of statutory preemption rights must both be renewed by the shareholders at least every five years, and we cannot provide any assurance that these authorizations will always be approved, which could limit our ability to issue equity and thereby adversely affect the holders of our securities.

***We have broad discretion in the use of our funds and may not use them effectively.***

We have broad discretion in the application of our available funds and could spend the funds in ways that do not improve our results of operations or enhance the value of our ordinary shares. Our failure 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 ordinary shares to decline and delay the development of our product candidates. Pending their use, we may invest funds in a manner that does not produce income or that loses value.

**Item 2. Properties.**

Our headquarters are located in Dublin, Ireland, where we lease approximately 5,551 square feet of office space. Our lease extends through November 2026, and we have the option to terminate the lease in November 2021 with one year's notice and a six months' rent penalty. In June 2018 we entered into a lease for a commercial unit in Dublin that extends through June 2038, with the option to terminate the lease in June 2028 with no penalty provided one year's notice is given. We also lease office space in Old Saybrook, Connecticut. Our lease extends through June 2022, and we have the option to extend the term of the lease for such space through June 2025. We also lease office space in Chicago, Illinois. Our lease extends through June 2023, and we have the option to extend the term of the lease for such space through June 2028. We believe that our current facilities are adequate to meet our near-term needs, and that suitable additional or substitute space will be available as needed on commercially reasonable terms.

**Item 3. Legal Proceedings.**

From time to time, we may be involved in legal proceedings or be subject to claims arising out of our operations. We are not currently a party to any legal proceedings that in the opinion of our management, would have a material adverse effect on our business.

**Ite m 4. Mine Safety Disclosures.**

Not applicable.

## PART II

### Item 5. Market for Registrant's Common Equity, Related Shareholder Matters and Issuer Purchases of Equity Securities.

**Market Information**

Our ordinary shares have been publicly traded on The Nasdaq Global Market under the symbol "ITRM" since May 25, 2018. Prior to that time, there was no public market for our shares.

**Holders of Record**

On February 28, 2019, we had approximately 22 shareholders of record of our ordinary shares. The actual number of shareholders is greater than this number of record holders and includes shareholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees.

**Dividends**

We have never declared or paid cash dividends on our ordinary shares and do not anticipate paying any dividends on our ordinary shares in the foreseeable future. Any determination to pay dividends in the future will be at the sole discretion of our board of directors after considering our financial condition, results of operations, capital requirements, contractual restrictions, general business conditions and other factors our board of directors deem relevant, and subject to compliance with applicable laws, including Irish Company law which requires Irish companies to have distributable reserves available for distribution equal to or greater than the amount of the proposed dividend. In addition, our ability to pay cash dividends is currently prohibited by the terms of our credit facility with SVB.

**Recent Sales of Unregistered Securities**

From January 1, 2018 through December 31, 2018, we sold and issued the following unregistered securities, which share numbers have been adjusted, as appropriate, for the one for 15.71 reverse stock split of our ordinary shares that became effective on May 15, 2018:

- On February 16, 2018, we issued an aggregate of 1,709,650 Series B-2 preferred shares at a purchase price of $18.85 per share for an aggregate purchase price of $32.2 million to existing holders of our series B-1 shares. Upon the closing of our IPO, all such Series B-2 preferred shares converted into ordinary shares, as described in Note 8 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

- On December 14, 2018, we issued 190,615 ordinary shares to a supplier at a price of $7.14 per share for an aggregate subscription price of $1.36 million pursuant to the terms of a subscription agreement with the supplier, as described in Note 8 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K. Our wholly owned subsidiary, Iterum Therapeutics International Limited, paid such aggregate subscription price to us in satisfaction of the suppliers obligation to pay the subscription monies to us and Iterum Therapeutics International Limited's obligation to pay certain amounts due and owing under certain commercial agreements entered into between such subsidiary and the supplier.

The issuances of these securities were exempt from registration under Section 4(a)(2) of the Securities Act (or Regulation D promulgated thereunder) in that the transactions were by an issuer not involving any public offering or were exempt from the registration requirements of the Securities Act in reliance on Regulation S promulgated under the Securities Act on the basis that the shares will not be offered, sold, pledged or transferred in the United States or to a U.S. person for a defined period.

The Company did not pay or give, directly or indirectly, any commission or other remuneration, including underwriting discounts and commissions, in connection with any of the issuances of securities listed above. All of the foregoing securities were deemed restricted securities for purposes of the Securities Act at the time of issue.

**Use of Proceeds from Registered Securities**

On May 30, 2018, we completed the IPO of our ordinary shares pursuant to which we issued and sold 6,150,000 ordinary shares at a price to the public of $13.00 per share. In addition, on June 26, 2018, we issued and sold an additional 200,000 ordinary shares at the IPO price of $13.00 per share as a result of the partial exercise by the underwriters of their option to purchase additional ordinary shares.

The offer and sale of all of the ordinary shares in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1 (File No. 333-224582), which was declared effective by the SEC on May 24, 2018.

We received aggregate gross proceeds from ourIPO of $82.5 million, or aggregate net proceeds of $74.2 million after deducting underwriting discounts and commissions of $5.8 million and offering costs of $2.5 million. None of the underwriting discounts and commissions or offering expenses were incurred or paid toour directors or officers or their associates or to persons owning 10% or more of our ordinary shares or to any of our affiliates.

As of December 31, 2018 we had used approximately $56.2 million from our IPO proceeds, including clinical milestone payments totaling $15.0 million paid to Pfizer pursuant to the exclusive license agreement we have entered into with Pfizer. There has been no material change in our planned use of the net proceeds from the IPO as described in our final prospectus filed pursuant to Rule 424(b)(4) under the Securities Act with the SEC on May 25, 2018.

**Purchases of Equity Securities by the Issuer**

None.

**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 the related notes and the other financial information included elsewhere 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 pharmaceutical company dedicated to developing and commercializing sulopenem to be potentially the first and only oral and intravenous (IV) branded penem available globally. Penems, including thiopenems and carbapenems, belong to a class of antibiotics more broadly defined as ß-lactam antibiotics, the original example of which was penicillin, but which now also includes cephalosporins. Sulopenem is a potent, thiopenem antibiotic delivered intravenously which is active against bacteria that belong to the group of organisms known as gram-negatives and cause urinary tract and intra-abdominal infections. We have successfully developed sulopenem in an oral tablet formulation, sulopenem etzadroxil-probenecid, which we refer to herein as oral sulopenem. Both sulopenem product candidates have the potential to be important new treatment alternatives to address growing concerns related to antibacterial resistance without the known toxicities of some of the most widely used antibiotics, specifically fluoroquinolones. We see two distinct opportunities for our sulopenem program: patients at elevated risk for treatment failure in the community setting suffering from uncomplicated urinary tract infections (uUTI) and hospitalized patients suffering from complicated, antibiotic-resistant infections.

During the third quarter of 2018, we initiated all three clinical trials in our Phase 3 development program which includes: a Phase 3 uUTI clinical trial, known as SUlopenem for Resistant Enterobacteriaceae (SURE) 1, comparing oral sulopenem to oral ciprofloxacin in women with uUTI, a Phase 3 complicated urinary tract infections (cUTI) clinical trial known as SURE 2, comparing IV sulopenem followed by oral sulopenem to IV ertapenem followed by oral ciprofloxacin in adults with cUTI and a Phase 3 complicated intra-abdominal infections (cIAI) clinical trial known as SURE 3, comparing IV sulopenem followed by oral sulopenem to IV ertapenem followed by a combination of oral ciprofloxacin and oral metronidazole in adults with cIAI. We designed one Phase 3 clinical trial in each indication based on our end of Phase 2 meeting with the U.S. Food and Drug Administration (FDA) and feedback from the European Medicines Agency (EMA). We are conducting the Phase 3 clinical trials under Special Protocol Assessment (SPA) agreements from the FDA. We expect to complete enrollment and produce topline data for all three clinical trials in the second half of 2019, and submit our new drug applications (NDAs) to the FDA by the end of 2019.

On May 30, 2018 we completed an initial public offering, or IPO, of our ordinary shares, and issued and sold 6,150,000 ordinary shares at a public offering price of $13.00 per share, resulting in net proceeds of $71.8 million after deducting underwriting discounts and commissions and offering costs payable by us. On June 26, 2018, we issued and sold an additional 200,000 ordinary shares at the IPO price of $13.00 per share pursuant to the underwriters' partial exercise of their option to purchase additional ordinary shares, resulting in additional net proceeds of $2.4 million after deducting underwriting discounts and commissions and offering costs payable by us. Aggregate net proceeds from the IPO totalled $74.2 million after deducting underwriting discounts and commissions and offering costs payable by us.

Since our inception, we have incurred significant operating losses. Our ability to generate product revenue sufficient to achieve profitability will depend heavily on the successful development and eventual commercialization of oral sulopenem and sulopenem. Our net losses for 2018, 2017 and 2016 were $77.1 million, $29.4 million and $13.5 million respectively. As of December 31, 2018, we had an accumulated deficit of $131.8 million. We expect to continue to incur significant expenses for the foreseeable future as we advance our sulopenem program through Phase 3 clinical trials, seek regulatory approval and engage in market preparation and pre-commercialization activities. In addition, if we obtain marketing approval for oral sulopenem and sulopenem, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. We are currently evaluating our commercialization strategy in the United States and other territories. We may also incur expenses in connection with the establishment of additional sources for the manufacture of sulopenem tablets and IV vials or the in-license or acquisition of additional product candidates. Additionally, we have incurred and expect to incur additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses that we did not incur as a private company.

As a result, we will require additional capital to fund our operations, to continue to develop our sulopenem program and to execute our strategy. Until such time as we can obtain marketing approval for oral sulopenem, sulopenem or any future product candidate and generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaboration agreements, other third-party funding, strategic alliances, licensing arrangements,

marketing and distribution arrangements or government funding. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back or discontinue the development and commercialization of our sulopenem program, or otherwise change our strategy.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2018, we had cash, cash equivalents, restricted cash and short-term investments of $84.7 million. We believe that our existing cash, cash equivalents, restricted cash, short-term investments and available borrowings under our credit facility, will enable us to fund our operating expenses and capital expenditure requirements through the first quarter of 2020. We have based these estimates on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. See the section titled "—Liquidity and Capital Resources."

**Components of Our Results of Operations**

***Revenue***

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from the sale of oral sulopenem or sulopenem in 2019. If our development efforts for our sulopenem program are successful and result in regulatory appro val and/or license agreements with third parties, we may generate revenue in the future from product sales. To date, all of our revenue has been derived from our Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator Award (CARB-X Award). We expect that our revenue in 2019 will be derived primarily from payments under the CARB-X Award or government awards that we may enter into in the future. In June 2017, CARB-X awarded us funds of up to $1.5 million to advance the development of our sulopenem program. We receive funding from CARB-X as we incur qualifying expenses. During the years ended December 31, 2018 and 2017 we recognized revenue of $0.9 million and $0.5 million, respectively, under this award.

***Operating Expenses***

*Research and Development Expenses*

Research and development expenses consist primarily of costs incurred in connection with the development of our sulopenem program, which include:

- expenses incurred under agreements with contract research organizations (CROs), contract manufacturing organizations (CMOs), as well as investigative sites and consultants that conduct our clinical trials, preclinical studies and other scientific development services;
- manufacturing scale-up expenses and the cost of acquiring and manufacturing preclinical and clinical trial materials and commercial materials, including manufacturing validation batches;
- employee-related expenses, including salaries, related benefits, travel and share-based compensation expense for employees engaged in research and development functions;
- costs related to compliance with regulatory requirements;
- facilities costs, depreciation and other expenses, which include rent and utilities; and
- payments made in cash, equity securities or other forms of consideration under third-party licensing agreements.

We expense research and development costs as incurred. Advance payments we make for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers.

Research and development activities are central to our business model. Product candidates in advanced stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later stage clinical trials. As a result, we expect that our research and development expenses will increase substantially in 2019 as we increase personnel costs, including share-based compensation, substantially complete the Phase 3 clinical trials for our sulopenem program, conduct other clinical trials and prepare regulatory filings for oral sulopenem and sulopenem. Clinical milestone payments totaling $15.0 million were paid to Pfizer, Inc., or Pfizer, with whom we have entered into an exclusive license agreement to in-license certain patent rights and know-how related to oral sulopenem and certain know-how related

to sulopenem IV (the "Pfizer License"), upon first patient dosing in a Phase 3 trial for oral sulopenem and sulopenem. These milestone payments were recorded in research and development expense in the consolidated statement of operations and comprehensive loss.

The successful development and commercialization of oral sulopenem and sulopenem is highly uncertain. At this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to complete the clinical development of our sulopenem program or when, if ever, material net cash inflows may commence from any of our product candidates. This uncertainty is due to the numerous risks and uncertainties associated with product development and commercialization, including the uncertainty of:

- the scope, progress, outcome and costs of our clinical trials and other research and development activities;
- successful patient enrollment in, and the initiation and completion of, clinical trials;
- the timing, receipt and terms of any marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- development and timely delivery of commercial drug formulations (i) that can be used in our clinical trials; and (ii) that are available for commercial launch;
- obtaining, maintaining, defending and enforcing patent claims and other intellectual property rights;
- significant and changing government regulation;
- launching commercial sales of our product candidates, if and when approved, whether alone or in collaboration with others; and
- maintaining a continued acceptable safety profile of the product candidates following approval.

We may never succeed in achieving regulatory approval for any of our product candidates. We may obtain unexpected results from our clinical trials. We may elect to discontinue, delay or modify clinical trials of some product candidates or focus on others. Any changes in the outcome of any of these variables with respect to the development of our product candidates in clinical development could mean a significant change in the costs and timing associated with the development of these product candidates. For example, if we experience significant delays in enrollment in any of our ongoing or planned clinical trials, or are required to add additional patients to a study to remain consistent with our original trial design assumptions, we could be required to expend significant additional financial resources and time on the completion of clinical development of that product candidate.

*General and Administrative Expenses*

General and administrative expenses consist primarily of salaries, related benefits, travel and share-based compensation expense for personnel in executive, finance, market research and administrative functions. General and administrative expenses also include director compensation and travel expenses, insurance, professional fees for legal, patent, consulting, accounting and audit services and market preparation expenses.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support the continued development of our sulopenem program. We also anticipate that we will incur increased accounting, audit, legal, regulatory, compliance, director compensation, director and officer insurance costs as well as investor and public relations expenses associated with being a public company. Additionally, if and when we believe regulatory approval of oral sulopenem and sulopenem appears likely, we anticipate an increase in payroll and expenses as a result of our preparation for commercial operations.

*Interest (Expense) Income, Net*

Interest (expense) income, net consists of interest paid and amortization of debt costs on our loan from Silicon Valley Bank (SVB), partially offset by interest earned on our cash and cash equivalents, which are generally invested in money market accounts, as well as interest earned on our investments in marketable securities.

*Other Income, Net*

Other income, net consists of realized and unrealized gains on our investments in marketable securities, partially offset by realized and unrealized foreign currency gains (losses) incurred in the normal course of business based on movement in the applicable exchange rates.

***Provision for Income Taxes***

We recognize income taxes under the asset and liability method. Deferred income taxes are recognized for differences between the financial reporting and tax bases of assets and liabilities at enacted statutory tax rates in effect for the years in which the differences are expected to reverse. The effect on deferred taxes of a change in tax rates is recognized in income in the period that includes the enactment date. In evaluating our ability to recover our deferred tax assets, we consider all available positive and negative evidence including past operating results, the existence of cumulative income in the most recent fiscal years, changes in the business in which we operate and our forecast of future taxable income. In determining future taxable income, we are responsible for assumptions utilized including the amount of Irish, U.S. and other foreign pre-tax operating income, the reversal of temporary differences and the implementation of feasible and prudent tax planning strategies. These assumptions require significant judgment about the forecasts of future taxable income and are consistent with the plans and estimates that we are using to manage the underlying business.

Valuation allowances are provided if it is more likely than not that some portion or all of the deferred tax assets will not be realized.

We account for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors including, but not limited to, changes in tax law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity and changes in facts or circumstances related to a tax position. We evaluate our tax positions on a quarterly basis. We also accrue for potential interest and penalties related to unrecognized tax benefits in income tax expense.

On December 22, 2017, the United States federal government enacted the Tax Act, marking a change from a worldwide tax system to a modified territorial tax system in the United States. As part of this change, the Tax Act, among other changes, provided a reduction of the U.S. federal corporate income tax rate from 34% to 21%, an indefinite carryforward of net operating losses incurred in 2018 and future periods, and an interest limitation starting in 2018 with an indefinite carryforward. Any impact to the Company related to these items were accounted for in the 2017 and 2018 tax provisions with minimal impact.

**Critical Accounting Policies and Significant Judgments and Estimates**

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States. The preparation of our consolidated financial statements and related disclosures requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenue, costs and expenses, and the disclosure of contingent assets and liabilities in our financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are 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. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

***Accrued Research and Development Expenses***

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf 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 actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of these estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- vendors, including central laboratories, in connection with preclinical development activities;
- CROs and investigative sites in connection with preclinical studies and clinical trials; and
- CMOs in connection with drug substance and drug product formulation of preclinical and clinical trial materials.

We base our expenses related to preclinical studies and clinical trials on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple research institutions and CROs that conduct and manage preclinical studies and clinical trials 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 expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed 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 the estimate, we adjust the accrual or the amount of prepaid expenses accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

***Share-Based Compensation***

We measure share options and other share-based awards granted to employees and directors based on the fair value on the date of the grant and recognize the corresponding compensation expense of those awards over the requisite service period, which is generally the vesting period of the respective award. We have issued share awards with both service-based and performance-based vesting conditions and record the expense for these awards over the requisite service or performance periods.

For share-based awards granted to consultants and non-employees, we recognize compensation expense over the period during which services are rendered by such consultants and non-employees until completed. At the end of each financial reporting period prior to completion of the service, the fair value of these awards is remeasured using the then-current fair value of our ordinary shares and updated assumption inputs in the Black-Scholes option-pricing model.

We estimate the fair value of each share option grant using the Black-Scholes option-pricing model, which uses as inputs the fair value of our ordinary shares and assumptions we make for the volatility of our ordinary shares, the expected term of our share options, the risk-free interest rate for a period that approximates the expected term of our share options and our expected dividend yield.

*Determination of the Fair Value of Ordinary Shares prior to IPO*

Since our IPO in May 2018, the fair value of our ordinary shares has been determined based on the quoted market price of our ordinary shares. Prior to our IPO, the estimated fair value of our ordinary shares was determined by our board of directors as of the date of each option grant, with input from management, considering our most recently available third-party valuation of our ordinary shares as well as our board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent third-party valuation through the date of the grant. Our board of directors considered various objective and subjective factors to determine the fair value of our ordinary shares as of each grant date, including:

- the prices at which we sold preferred shares and the superior rights and preferences of the preferred shares relative to our ordinary shares at the time of each grant;
- the progress of our research and development programs, including the status of preclinical studies and clinical trials for our product candidates;
- our stage of development and commercialization and our business strategy;
- external market conditions affecting the pharmaceutical industry and trends within the pharmaceutical industry;
- our financial position, including cash on hand, and our historical and forecasted performance and operating results;
- the lack of an active public market for our ordinary shares and our preferred shares;
- the likelihood of achieving a liquidity event, such as an initial public offering or a sale of our company in light of prevailing market conditions; and
- the analysis of initial public offerings and the market performance of similar companies in the pharmaceutical and biotechnology industries.

Our third-party valuations of ordinary shares were prepared using the option-pricing method (OPM), which used an income and market approach to estimate our enterprise value. The OPM treats ordinary shares and preferred shares as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the ordinary shares have value only if the funds available for distribution to shareholders exceeded the value of the preferred share liquidation preferences at the time of the liquidity event, such as a strategic sale

or a merger. Discounts for lack of control and marketability of the ordinary shares were applied directly or were inherentin the methodologies employed to arrive at an indication of the value for the ordinary shares.

The assumptions underlying these valuations represent management's best estimates, which involve inherent uncertainties and the application of management judgment. As a result, if factors or expected outcomes change and we use significantly different assumptions or estimates, our share-based compensation expense could be materially different.

**Results of Operations**

***Comparison of the Years Ended December 31, 2018 and 2017***

The following table summarizes our operating losses for the years ended December 31, 2018 and 2017:

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | Change |
| | (In thousands) | | |
| Revenue | $ 869 | $ 508 | $ 361 |
| Operating expenses: | | | |
| Research and development | 68,647 | 25,499 | 43,148 |
| General and administrative | 8,781 | 4,464 | 4,317 |
| Total operating expenses | $ 77,428 | $ 29,963 | $ 47,465 |
| Operating loss | $ (76,559) | $ (29,455) | $ (47,104) |

*Revenue*

In June 2017, CARB-X awarded us funds of up to $1.5 million to advance the development of our sulopenem program. We receive funding from CARB-X as we incur qualifying expenses. During the years ended December 31, 2018 and 2017, we recognized $0.9 million and $0.5 million of revenue, respectively, under this award.

*Research and Development Expenses*

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | Change |
| | (In thousands) | | |
| CRO and other preclinical, clinical trial and milestone related expenses | $ 41,415 | $ 4,665 | $ 36,750 |
| Chemistry, manufacturing and control (CMC) related expenses | 17,782 | 15,237 | 2,545 |
| Personnel related (including share-based compensation) | 8,211 | 3,527 | 4,684 |
| Consulting fees | 1,239 | 2,070 | (831) |
| Total research and development expenses | $ 68,647 | $ 25,499 | $ 43,148 |

The increase in CRO and other preclinical, clinical trial and milestone related expenses of $36.8 million was primarily due to costs incurred related to our three Phase 3 clinical trials, which initiated in the year, as well as an increase in preclinical and Phase 1 clinical trial activity. During the year, we made clinical milestone payments totaling $15.0 million to Pfizer, upon first patient dosing of oral sulopenem and sulopenem in a Phase 3 clinical trial. These milestone payments were recorded as research and development expenses. CMC related expenses increased by $2.5 million primarily due to process validation activities necessary for our regulatory filings. Personnel related expenses increased by $4.7 million as a result of an increase in headcount in our clinical development, CMC and regulatory functions. Personnel related expenses for the years ended December 31, 2018 and 2017 included share-based compensation expense of $0.4 million and $0.1 million, respectively. The decrease in consulting fees of $0.8 million was primarily due to the increase in employee headcount, reducing our need for outside consultants.

*General and Administrative Expenses*

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | Change |
| | (In thousands) | | |
| Personnel related (including share-based compensation) | $ 4,504 | $ 2,463 | $ 2,041 |
| Professional and consultant fees | 2,202 | 929 | 1,273 |
| Facility related and other | 2,075 | 1,072 | 1,003 |
| Total general and administrative expenses | $ 8,781 | $ 4,464 | $ 4,317 |

Personnel related expenses increased by $2.0 million as a result of an increase in headcount in our general and administrative function. Personnel related expenses for the years ended December 31, 2018 and 2017 included share-based compensation expense of $0.9 million and $0.3 million, respectively. Professional and consulting fees increased by $1.3 million as a result of pre-commercialization activities. Facility related and other costs increased by $1.0 million primarily as a result of higher lease charges relating to our offices, increased insurance related costs and higher board of directors compensation.

***Comparison of the Years Ended December 31, 2017 and 2016***

The following table summarizes our operating losses for the years ended December 31, 2017 and 2016:

| | Year ended December 31, | | |
|---|---|---|---|
| | 2017 | 2016 | Change |
| | (In thousands) | | |
| Revenue | $ 508 | $ — | $ 508 |
| Operating expenses: | | | |
| Research and development | 25,499 | 10,101 | 15,398 |
| General and administrative | 4,464 | 3,258 | 1,206 |
| Total operating expenses | $ 29,963 | $ 13,359 | $ 16,604 |
| Operating loss | $ (29,455) | $ (13,359) | $ (16,096) |

*Revenue*

In June 2017, CARB-X awarded us funds of up to $1.5 million to advance the development of our sulopenem program. We receive funding from CARB-X as we incur qualifying expenses. During the year ended December 31, 2017, we recognized $0.5 million of revenue under this award.

*Research and Development Expenses*

| | Year ended December 31, | | |
|---|---|---|---|
| | 2017 | 2016 | Change |
| | (In thousands) | | |
| Chemistry, manufacturing and control (CMC) related expenses | $ 15,237 | $ 4,030 | $ 11,207 |
| CRO and other preclinical and clinical trial related expenses | 4,665 | 2,894 | 1,771 |
| Personnel related (including share-based compensation) | 3,527 | 1,717 | 1,810 |
| Consulting fees | 2,070 | 1,460 | 610 |
| Total research and development expenses | $ 25,499 | $ 10,101 | $ 15,398 |

The increase in CMC related expenses of $11.2 million was primarily due to formulation development, manufacturing process, and manufacturing of clinical trial material in anticipation of our Phase 3 clinical trials in the second half of 2018. CRO and other preclinical and clinical trial related expenses increased by $1.8 million due to increased Phase 1 clinical trial activity and a Ciprofloxacin Phase 4 clinical trial study. Personnel related expenses increased by $1.8 million as a result of an increase in headcount in our CMC, clinical development and regulatory functions. Personnel related expenses for the years ended December 31, 2017 and 2016 included share-based compensation expense of $0.1 million and $0.1 million, respectively. The increase in consulting fees of $0.6 million was primarily due to the increase in consultants used for preclinical and clinical trial activity.

*General and Administrative Expenses*

| | Year ended December 31, | | |
|---|---|---|---|
| | 2017 | 2016 | Change |
| | (In thousands) | | |
| Personnel related (including share-based compensation) | $ 2,463 | $ 2,003 | $ 460 |
| Professional and consultant fees | 929 | 903 | 26 |
| Facility related and other | 1,072 | 352 | 720 |
| Total general and administrative expenses | $ 4,464 | $ 3,258 | $ 1,206 |

The increase in facility related and other costs of $0.7 million was primarily due to the lease of office space in Dublin that we entered into at the end of 2016, software costs, director compensation and travel expenses, and general support costs for the increase in headcount. Personnel related expenses increased by $0.5 million as a result of an increase in headcount in our general and administrative function. Personnel related expenses for the years ended December 31, 2017 and 2016 included share-based compensation expense of $0.3 million and $0.2 million, respectively.

**Liquidity and Capital Resources**

Since our inception, we have incurred significant operating losses and negative cash flows from our operations. We have generated limited revenue to date from a funding arrangement with CARB-X Award. We have funded our operations to date primarily with proceeds from the sale of preferred shares and ordinary shares, debt raised under our financing arrangement with SVB and payments received under the funding arrangement with CARB-X. Through December 31, 2018, we had received cash proceeds of $195.1 million from sales of our Series A and Series B preferred shares and ordinary shares and $15.0 million from the first drawdown of our SVB loan. As of December 31, 2018, we had cash, cash equivalents, restricted cash and short-term investments of $84.7 million.

***Secured credit facility***

On April 27, 2018, our subsidiaries, Iterum Therapeutics International Limited, Iterum Therapeutics US Holding Limited and Iterum Therapeutics US Limited (Borrowers) entered into a loan and security agreement with SVB pursuant to which SVB agreed to lend the Borrowers up to $30.0 million in two term loans. $15.0 million of the secured credit facility was funded on closing and the other $15.0 million is available at our option upon the satisfaction of either of the following conditions which we refer to as the Second Draw Conditions: (i) the achievement of both non-inferiority and superiority primary endpoints from our Phase 3 clinical uUTI trial and reporting satisfactory safety data; or (ii) the achievement of non-inferiority primary endpoints from both our Phase 3 uUTI and cUTI clinical trials as well as reporting satisfactory safety data, in each case as determined by SVB at its sole discretion. Our option to draw the second term loan will terminate upon the earliest to occur of October 31, 2019, the thirtieth day following the occurrence of either of the Second Draw Conditions, or the occurrence of an event of default. A non-utilization fee of 1.50% of the aggregate undrawn principal amount shall apply if we satisfy the Second Draw Conditions but choose not to draw down the second term loan. The principal borrowed under the secured credit facility bears interest at a floating per annum rate equal to the greater of (i) 8.31%; or (ii) 3.89% above the Wall Street Journal prime rate, which interest is payable monthly in arrears.

The initial draw requires monthly amortization payments commencing November 1, 2019, which will be extended to April 1, 2020 if the second draw is made. All outstanding principal, plus a 4.2% final payment fee, will be due and payable on the earliest to occur of March 1, 2022 (Maturity Date), the acceleration of either term loan or the prepayment of either term loan. The final payment fee of $0.6 million, which represents 4.2% of the funded loan, is accreted using the effective interest method over the life of the loan as interest expense.

The secured credit facility draws are subject to prepayment fees of 3.00% in the first year, 2.00% in the second year and 1.00% thereafter in the event of prepayment at any time prior to the Maturity Date.

In connection with the initial $15.0 million draw, we issued SVB and Life Sciences Fund II LLC (LSF) warrants to purchase an aggregate of 19,890 Series B-2 preferred shares (which converted to ordinary shares in connection with our IPO) at an exercise price of $18.85 per share. If we draw down the second term loan, each of SVB and LSF will be entitled, pursuant to additional share warrants issued to each of them at closing, to purchase such number of additional ordinary shares in an aggregate amount equal to 2.50% of the funded amount, divided by the applicable exercise price. Obligations under the secured credit facility are secured by substantially all of our existing and future assets and the existing and future assets of our subsidiaries, including intellectual property.

***Cash Flows***

The following table summarizes our cash flows for each of the periods presented:

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | 2016 |
| | (In thousands) | | |
| Net cash used in operating activities | $ (75,890) | $ (30,604) | $ (11,298) |
| Net cash used in investing activities | (8,658) | (31,587) | — |
| Net cash provided by financing activities | 120,842 | 45,867 | 20,851 |
| Effect of exchange rates on cash and cash equivalents | (108) | — | — |
| Net increase / (decrease) in cash | $ 36,186 | $ (16,324) | $ 9,553 |

*Operating Activities*

During the year ended December 31, 2018, operating activities used $75.9 million of cash, resulting from our net loss of $77.1 million and net cash used by changes in our operating assets and liabilities of $1.6 million, partially offset by non-cash charges of $2.8 million. Net cash used by changes in our operating assets and liabilities for the year ended December 31, 2018 consisted primarily of increases in prepaid expenses and other current assets, largely related to advance payments to contract research organizations, and other assets, largely related to a deposit paid for the Dublin commercial lease and advance payments to CMOs, partially offset by increases in accounts payable and accrued expenses, primarily due to an increase in clinical trial expenses.

During the year ended December 31, 2017, operating activities used $30.6 million of cash, resulting from our net loss of $29.4 million and net cash used by changes in our operating assets and liabilities of $1.6 million, partially offset by non-cash charges of $0.4 million. Net cash used by changes in our operating assets and liabilities for the year ended December 31, 2017 consisted of increases in prepaid expenses and other assets primarily related to advance payments to CMOs, partially offset by increases in accrued expenses and accounts payable primarily due to increases in clinical trial supply and costs.

During the year ended December 31, 2016, operating activities used $11.3 million of cash, resulting from our net loss of $13.5 million, partially offset by non-cash charges of $0.4 million and net cash provided by changes in our operating assets and liabilities of $1.8 million. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2016 consisted primarily of increases in accrued expenses and accounts payable primarily due to increases in clinical trial supply and costs, partially offset by increases in prepaid expenses and other assets primarily related to advance payments to CMOs.

*Investing Activities*

During the year ended December 31, 2018, net cash used in investing activities of $8.7 million was primarily related to purchases of short-term investments of $96.5 million and purchases of property and equipment of $0.1 million, partially offset by sales of short-term investments of $87.9 million. During the year ended December 31, 2017, net cash used in investing activities of $31.6 million was primarily related to purchases of short-term investments of $53.3 million and fixed asset purchases of $0.8 million, partially offset by sales of short-term investments of $22.5 million. We did not use any cash for investing activities during the year ended December 31, 2016.

*Financing Activities*

During the year ended December 31, 2018 net cash provided by financing activities was $120.8 million and consisted of net cash proceeds from the issuance of Series B-2 preferred shares in February 2018 (which converted to ordinary shares in connection with our IPO) of $32.2 million, net cash proceeds from the issuance of ordinary shares in May and June 2018 associated with our IPO of $74.2 million and net cash proceeds from the SVB loan drawdown of $14.4 million. During the year ended December 31, 2017, net cash provided by financing activities was $45.9 million, and consisted of gross cash proceeds from the issuance of Series B-1 preferred shares in May 2017. During the year ended December 31, 2016, net cash provided by financing activities was $20.9 million, and consisted of gross cash proceeds from the issuance of Series A preferred shares in December 2016.

***Funding Requirements***

We expect to continue to incur significant expenses and increasing operating losses as we conduct our ongoing and planned clinical trials of oral sulopenem and sulopenem, seek marketing approval for such product candidates if clinical trials are successful, and pursue the development of our sulopenem program in additional indications through preclinical and clinical development. Our expenses will also increase substantially if and as we:

- conduct additional clinical trials for oral sulopenem and sulopenem, which include our three ongoing Phase 3 clinical trials, and our ongoing and planned Phase 1 clinical trials, which we expect to occur through 2019;
- initiate other studies as part of our sulopenem program, some of which may be required for regulatory approval of our product candidates;
- establish a sales, marketing and distribution infrastructure to commercialize oral sulopenem and sulopenem in the United States if we obtain marketing approval from the U.S. Food and Drug Administration (FDA) and we choose to commercialize directly in the United States;
- establish manufacturing and supply chain capacity sufficient to provide commercial quantities of oral sulopenem and sulopenem, if we obtain marketing approval;
- pursue the development of our sulopenem program in additional indications;
- maintain, expand, defend and protect our intellectual property portfolio;
- hire additional clinical, scientific and commercial personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts, as well as to support our ongoing transition to a public reporting company; and
- acquire or in-license other product candidates or technologies.

We believe that our existing cash, cash equivalents, restricted cash, short-term investments and available borrowings under our credit facility, will enable us to fund our operating expenses and capital expenditure requirements through the first quarter of 2020. We have based these estimates on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect. We expect that we will require additional capital to file with regulatory agencies and commercialize oral sulopenem and sulopenem, if we receive regulatory approval, and to pursue in-licenses or acquisitions of other product candidates. If we receive regulatory approval for oral sulopenem or sulopenem, we expect to incur significant commercialization expenses related to product manufacturing, sales, marketing and distribution, depending on where we choose to commercialize.

Because of the numerous risks and uncertainties associated with research, development and commercialization of pharmaceutical product candidates, we are unable to estimate the exact amount of our working capital requirements. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the timing and costs of our ongoing clinical trials of oral sulopenem and sulopenem, including our three Phase 3 clinical trials in our three initial indications;
- the initiation, progress, timing, costs and results of preclinical studies and clinical trials of other potential product candidates and of our current product candidates in additional indications;
- the amount of funding that we receive under government awards that we have applied for or may apply for in the future;
- the number and characteristics of product candidates that we pursue;
- the outcome, timing and costs of seeking regulatory approvals;
- the costs of commercialization activities for oral sulopenem and sulopenem and other product candidates if we receive marketing approval, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- the receipt of marketing approval and revenue received from any potential commercial sales of oral sulopenem and sulopenem;
- the terms and timing of any future collaborations, licensing 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 pursuant to the Pfizer License or other future license agreements;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against any intellectual property related claims;
- the costs of operating as a public company; and
- the extent to which we in-license or acquire other products and technologies.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through a combination of public or private equity offerings, debt financings, collaboration agreements, other third-party funding, strategic alliances, licensing arrangements, marketing and distribution arrangements or government funding. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our shareholders' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our ordinary shareholders. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. Our secured credit facility with SVB imposes operating and other restrictions on us. Such restrictions affect, and in many cases limit or prohibit, our ability to dispose of certain assets, pay dividends and incur additional indebtedness, among other things. If we raise additional funds through other third-party funding, collaboration agreements, strategic alliances, licensing arrangements or marketing and distribution arrangements, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

**Contractual Obligations and Commitments**

The following table summarizes our contractual obligations as of December 31, 2018, and the effects that such obligations are expected to have on our liquidity and cash flows in future periods:

| | Payments Due by Period | | | | |
|---|---|---|---|---|---|
| | Total | Less than 1 year | 1 to 3 years | 3 to 5 years | More than 5 years |
| | (In thousands) | | | | |
| Operating lease commitments (1) | $ 7,061 | $ 904 | $ 2,050 | $ 1,751 | $ 2,356 |
| Principal loan repayments | 15,000 | 1,034 | 12,414 | 1,552 | — |
| Total | $ 22,061 | $ 1,938 | $ 14,464 | $ 3,303 | $ 2,356 |

(1) Reflects payments due for our leases of office space and a commercial facility under operating lease agreements that expire in 2022, 2023, 2026 and 2028.

Under the Pfizer License, we have agreed to make certain regulatory and sales milestone payments, pay royalties and make a potential one-time payment related to sublicensing income that exceeds a certain threshold. We have not included any contingent payment obligations, such as milestones, royalties, or one-time payments, in the table above as the amount, timing and likelihood of such payments are not known. We are obligated to pay Pfizer royalties ranging from a single-digit to mid-teens percentage based on marginal net sales of each licensed product.

In June 2016, we entered into an agreement with a supplier whereby we agreed to pay $2.9 million to the supplier to acquire equipment, which will be used solely to manufacture pro duct for us. In June 2018, we entered into a supplemental agreement with this supplier whereby we agreed to pay an additional $2.3 million for additional equipment and dedicated personnel under the same terms of the original agreement. These payments will be offset against the price of the product to be supplied under a future supply agreement. As of December 31, 2018, $1.6 million remained outstanding to the supplier.

**Emerging Growth Company Status**

The Jumpstart Our Business Startups Act of 2012 permits an “emerging growth company” such as us to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have irrevocably elected to “opt out” of this provision and, as a result, we will comply with new or revised accounting standards when they are required to be adopted by public companies that are not emerging growth companies.

**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 in the rules and regulations of the Securities and Exchange Commission (SEC).

**Recently Issued Accounting Pronouncements**

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 2 to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

**Item 7A. Quantitative and Qualitative Disclosures About Market Risk.**

As of December 31, 2018, we had cash, cash equivalents and marketable securities of $84.6 million, consisting of cash, commercial paper, U.S. treasury bills and agency bonds. The primary objectives of our investment activities are to preserve principal, provide liquidity and maximize income without significantly increasing risk. Due to the short-term nature of our portfolio we do not believe an immediate interest rate increase of 100 basis points would have a material effect on the fair market value of our portfolio, and, accordingly, we do not expect our operating results or cash flows to be materially affected by a sudden change in market interest rates.

We contract with CROs and CMOs globally. We may be subject to fluctuations in foreign currency rates in connection with certain of these agreements. Transactions denominated in currencies other than the functional currency are recorded based on exchange rates at the time such transactions arise. As of December 31, 2018 and 2017, substantially all of our liabilities were denominated in U.S. dollars. Realized net foreign currency gains and losses did not have a material effect on our results of operations for the years ended December 31, 2018, 2017 and 2016.

The interest rate on our secured credit facility is sensitive to changes in interest rates. Interest accrues at a per annum rate equal to the greater of (i) 8.31%; or (ii) 3.89% above The Wall Street Journal prime rate. The Wall Street Journal prime rate increased from 4.75% to 5.00% on June 14, 2018, to 5.25% on September 27, 2018 and to 5.50% on December 20, 2018.

**Item 8. Financial Statements and Supplementary Data.**

**ITERUM THERAPEUTICS PLC**

**INDEX TO CONSOLIDATED FINANCIAL STATEMENTS**

**Report of Independent Registered Public Accounting Firm**

To the Shareholders and Board of Directors
Iterum Therapeutics plc.:

*Opinion on the Consolidated Financial Statements*

We have audited the accompanying consolidated balance sheets of Iterum Therapeutics plc and subsidiaries (the Company) as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, convertible preferred shares and shareholders' equity and cash flows for each of the years in the three-year period ended December 31, 2018, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the years in the three-year period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

*Basis for Opinion*

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (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 consolidated 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 consolidated 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 consolidated 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 consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

*/s/ KPMG*

We have served as the Company's auditor since 2015.

Dublin, Ireland
March 25, 2019

**ITERUM THERAPEUTICS PLC**
**Consolidated Balance Sheets**
(In thousands, except share and per share data)

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| **Assets** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 44,551 | $ 8,485 |
| Short-term investments | 40,000 | 30,731 |
| Prepaid expenses and other current assets | 8,390 | 4,957 |
| Current portion of restricted cash | 30 | — |
| Total current assets | 92,971 | 44,173 |
| Property and equipment, net | 700 | 747 |
| Restricted cash, less current portion | 90 | — |
| Other assets | 4,110 | 1,837 |
| **Total assets** | $ 97,871 | $ 46,757 |
| **Liabilities, Convertible Preferred Shares and Shareholders' Equity** | | |
| Current liabilities: | | |
| Accounts payable | $ 4,041 | $ 3,152 |
| Accrued expenses | 7,046 | 3,974 |
| Current portion of long-term debt | 1,019 | — |
| Income taxes payable | 113 | — |
| Total current liabilities | 12,219 | 7,126 |
| Long-term debt, less current portion | 13,079 | — |
| Other liabilities | 951 | 80 |
| Total liabilities | $ 26,249 | $ 7,206 |
| Commitments and contingencies *(Note 11)* | | |
| Series A convertible preferred shares, $0.01 par value per share: no shares authorized or issued at December 31, 2018; 3,032,463 shares authorized, 3,032,457 shares issued at December 31, 2017 | — | 30 |
| Series B convertible preferred shares, $0.01 par value per share: no shares authorized or issued at December 31, 2018; 3,696,943 shares authorized, 2,654,206 shares issued at December 31, 2017 | — | 27 |
| Shareholders' equity: | | |
| Ordinary shares, $0.01 par value per share: 50,000,000 shares authorized, 14,352,046 shares issued at December 31, 2018; 7,956,715 shares authorized, 413,110 shares issued at December 31, 2017 | 144 | 4 |
| Additional paid-in capital | 203,271 | 94,227 |
| Accumulated deficit | (131,793 ) | (54,737 ) |
| Total shareholders' equity | 71,622 | 39,494 |
| **Total liabilities, convertible preferred shares and shareholders' equity** | $ 97,871 | $ 46,757 |

The accompanying notes are an integral part of these consolidated financial statements

**ITERUM THERAPEUTICS PLC**
**Consolidated Statements of Operations and Comprehensive Loss**
(In thousands, except share and per share data)

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | 2016 |
| Revenue | $ 869 | $ 508 | $ — |
| Operating expenses: | | | |
| Research and development | (68,647) | (25,499) | (10,101) |
| General and administrative | (8,781) | (4,464) | (3,258) |
| Total operating expenses | (77,428) | (29,963) | (13,359) |
| Operating loss | (76,559) | (29,455) | (13,359) |
| Interest (expense) / income, net | (426) | 277 | - |
| Other income, net | 401 | 216 | 8 |
| Total other (expense) / income | (25) | 493 | 8 |
| Loss before income taxes | (76,584) | (28,962) | (13,351) |
| Income tax expense | (472) | (444) | (113) |
| Net loss and comprehensive loss | (77,056) | (29,406) | (13,464) |
| Net loss attributable to ordinary shareholders | $ (77,056) | $ (29,406) | $ (13,464) |
| Net loss per share attributable to ordinary shareholders – basic and diluted | $ (8.82) | $ (170.84) | $ (568.87) |
| Weighted average ordinary shares outstanding – basic and diluted | 8,734,109 | 172,130 | 23,668 |

The accompanying notes are an integral part of these consolidated financial statements

**ITERUM THERAPEUTICS PLC**
**Consolidated Statements of Convertible Preferred Shares and Shareholders' Equity**
(In thousands, except share and per share data)

| | Convertible Preferred Shares | | Ordinary Shares | | Preferred Shares to be issued | Additional Paid in Capital | Accumulated Deficit | Total |
|---|---|---|---|---|---|---|---|---|
| | Shares | Amount | Shares | Amount | | | | |
| Balance at December 31, 2015 | 1,514,320 | $ 15 | 413,110 | $ 4 | $ 3,000 | $ 23,813 | $ (11,867) | $ 14,950 |
| Issuance of Series A convertible preferred shares | 1,518,137 | 15 | — | — | (3,000) | 23,834 | — | 20,834 |
| Share-based compensation expense | — | — | — | — | — | 348 | — | 348 |
| Net loss | — | — | — | — | — | — | (13,464) | (13,464) |
| Balance at December 31, 2016 | 3,032,457 | $ 30 | 413,110 | $ 4 | $ — | $ 47,995 | $ (25,331) | $ 22,668 |
| Issuance of Series B convertible preferred shares | 2,654,206 | 27 | — | — | — | 45,840 | — | 45,840 |
| Share-based compensation expense | — | — | — | — | — | 392 | — | 392 |
| Net loss | — | — | — | — | — | — | (29,406) | (29,406) |
| Balance at December 31, 2017 | 5,686,663 | $ 57 | 413,110 | $ 4 | $ — | $ 94,227 | $ (54,737) | $ 39,494 |
| Issuance of Series B convertible preferred shares, net of issuance costs | 1,709,650 | 17 | — | — | — | 32,159 | — | 32,159 |
| Issuance of ordinary shares on initial public offering, net of issuance costs | — | — | 6,350,000 | 64 | — | 74,089 | — | 74,153 |
| Exercise of share options | — | — | 2,008 | — | — | 7 | — | 7 |
| Issuance of ordinary shares under subscription agreement | — | — | 190,615 | 2 | — | 1,360 | — | 1,362 |
| Redenomination of share capital | — | 42 | — | (42) | — | — | — | (42) |
| Conversion of preferred shares to ordinary shares | (7,396,313) | (116) | 7,396,313 | 116 | — | — | — | 116 |
| Issuance of warrants for ordinary shares | — | — | — | — | — | 139 | — | 139 |
| Share-based compensation expense | — | — | — | — | — | 1,290 | — | 1,290 |
| Net loss | — | — | — | — | — | — | (77,056) | (77,056) |
| Balance at December 31, 2018 | — | $ — | 14,352,046 | $ 144 | $ — | $ 203,271 | $ (131,793) | $ 71,622 |

The accompanying notes are an integral part of these consolidated financial statements

**ITERUM THERAPEUTICS PLC**
**Consolidated Statements of Cash Flows**
(In thousands, except share and per share data)

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | 2016 |
| **Cash flows from operating activities:** | | | |
| Net loss | $ (77,056) | $ (29,406) | $ (13,464) |
| Adjustments to reconcile net loss to cash used in operating activities: | | | |
| Depreciation | 136 | 65 | — |
| Share-based compensation expense | 1,290 | 392 | 348 |
| Gain on short term investments | (423) | — | — |
| Non-cash (gain) / loss on short term investments | (278) | 44 | — |
| Interest on short-term investments | (40) | (95) | — |
| Amortization of debt discount and deferred financing costs | 360 | — | — |
| Issuance of ordinary shares under subscription agreement | 1,362 | — | — |
| Other | 362 | — | — |
| Changes in operating assets and liabilities: | | | |
| Prepaid expenses and other current assets | (3,613) | (3,815) | (966) |
| Other assets | (2,273) | (782) | (1,052) |
| Accounts payable | 849 | 1,671 | 1,188 |
| Accrued expenses | 3,072 | 1,236 | 2,665 |
| Income taxes | 120 | 6 | (17) |
| Other liabilities | 242 | 80 | — |
| Net cash used in operating activities | (75,890) | (30,604) | (11,298) |
| **Cash flows from investing activities:** | | | |
| Purchases of property and equipment | (90) | (812) | — |
| Purchases of short-term investments | (96,493) | (53,275) | — |
| Proceeds from sale of short-term investments | 87,925 | 22,500 | — |
| Net cash used in investing activities | (8,658) | (31,587) | — |
| **Cash flows from financing activities:** | | | |
| Proceeds from issuance of debt, net of debt issuance costs | 14,507 | — | — |
| Proceeds from issuance of Series A convertible preferred shares | — | — | 20,851 |
| Proceeds from issuance of Series B convertible preferred shares | 32,175 | 45,867 | — |
| Proceeds from issuance of ordinary shares on initial public offering, net of issuance costs | 74,153 | — | — |
| Proceeds from exercise of share options | 7 | — | — |
| Net cash provided by financing activities | 120,842 | 45,867 | 20,851 |
| Effect of exchange rates on cash and cash equivalents | (108) | — | — |
| Net increase / (decrease) in cash, cash equivalents and restricted cash | 36,186 | (16,324) | 9,553 |
| Cash, cash equivalents and restricted cash, at beginning of period | 8,485 | 24,809 | 15,256 |
| Cash, cash equivalents and restricted cash, at end of period | $ 44,671 | $ 8,485 | $ 24,809 |
| **Supplemental Disclosure of Cash Flow Information:** | | | |
| Income tax paid—U.S. | $ 352 | $ 439 | $ 130 |
| Interest paid | 809 | — | — |

The accompanying notes are an integral part of these consolidated financial statements

**(1) Nature of Operations and Basis of Presentation**

Iterum Therapeutics plc (the "Company") was incorporated under the laws of the Republic of Ireland in June 2015 as a limited company and re-registered as a public limited company on March 20, 2018. The Company maintains its registered office at Block 2 Floor 3, Harcourt Centre, Harcourt Street, Dublin 2, Ireland. The Company commenced operations in November 2015. The Company licensed global rights to its novel anti-infective compound, sulopenem, from Pfizer Inc. ("Pfizer"). The Company is a clinical-stage pharmaceutical company dedicated to developing and commercializing sulopenem to be potentially the first and only oral and intravenous ("IV") branded penem available globally.

Since inception, the Company has devoted substantially all of its efforts to research and development, recruiting management and technical staff, and raising capital, and has financed its operations through the issuance of ordinary and convertible preferred shares, debt raised under a financing arrangement with Silicon Valley Bank ("SVB") and a sub-award from the Trustees of Boston University under the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator ("CARB-X") program (the CARB-X Award). The Company has not generated any product revenue. The Company is subject to risks and uncertainties commo n to early-stage companies in the pharmaceutical industry, including, but not limited to, failure to successfully develop and commercialize its product candidates, development by competitors of new technological innovations, dependence on key personnel, protection of proprietary technology, compliance with government regulations and the ability to secure additional capital to fund operations. Product candidates currently under development will require significant additional research and development efforts, including preclinical and clinical testing and regulatory approval prior to commercialization.

Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") and include the accounts of the Company and its subsidiaries.

On May 15, 2018, the Company's shareholders approved a consolidation of its ordinary shares and convertible preferred shares at a 1-for-15.71 ratio (the "Reverse Share Split"), effective on that date. Fractional entitlements to ordinary shares and convertible preferred shares arising as a result of the Reverse Share Split were rounded down to the nearest whole number for each holder of ordinary shares and convertible preferred shares. Those fractional entitlements were aggregated and surrendered to the Company for cancellation. Immediately following the Reverse Share Split, the Company redenominated its ordinary shares and convertible preferred shares from $0.01571 (the nominal value resulting from the Reverse Share Split) per share to $0.01 per share (the "Renominalisation"). All issued and outstanding ordinary shares, convertible preferred shares, options for ordinary shares, restricted share awards, warrants and per share amounts have been retroactively adjusted to reflect this Reverse Share Split and Renominalisation for all periods presented.

On May 30, 2018, the Company completed an initial public offering ("IPO") of its ordinary shares, and issued and sold 6,150,000 ordinary shares at a public offering price of $13.00 per share, resulting in net proceeds of $71.8 million after deducting underwriting discounts and commissions and offering costs payable by the Company. On June 26, 2018, the Company issued and sold an additional 200,000 ordinary shares at the IPO price of $13.00 per share pursuant to the underwriters' partial exercise of their option to purchase additional ordinary shares, resulting in additional net proceeds of $2.4 million after deducting underwriting discounts and commissions and offering costs payable by the Company. Aggregate net proceeds from the IPO totaled $74.2 million after deducting underwriting discounts and commissions and offering costs payable by the Company.

In accordance with Accounting Standards Update ("ASU") 2014-15,*Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern (Subtopic 205-40)*, the Company has evaluated whether there are conditions and events, considered in aggregate, that raise substantial doubt about the Company's ability to continue as a going concern within one year of the date of issue of the consolidated financial statements.

The Company has incurred operating losses since inception, including net losses of $77.1 million, $29.4 million and $13.5 million for the years ended December 31, 2018, 2017 and 2016, respectively. The Company had an accumulated deficit of $131.8 million as of December 31, 2018. The Company expects to continue to incur net losses for the foreseeable future and is highly dependent on its ability to find additional sources of funding in the form of debt or equity financing to fund its operations. Management believe that its cash and cash equivalents balance of $44.6 million and short-term investments balance of $40.0 million at December 31, 2018, together with the $15.0 million potentially available under the secured credit facility with SVB, are sufficient

to fund operations for at least one year from the date theannual consolidated financial statements are issued. The $15.0 million will be available to the Company through October 31, 2019, upon satisfaction of either (i) the achievement by the Company of both non-inferiority and superiority primary endpoints from its Phase 3 uncomplicated urinary tract infection (uUTI) trial, as well as reporting satisfactory safety data from the trial, or (ii) the achievement of non-inferiority primary endpoints from both its Phase 3 uUTI and complicated urinary tract infection (cUTI) trials, as well as reporting satisfactory safety data from the trials. In making its assessment of the ability of the Company to continue as a going concern for twelve months from the date these financial statements are filed, management have considered the Company's available cash resources, future financings options available to the Company, the planned operations of the Company and the ability to adjust its plans if required. The inability to obtain funding, as and when needed, would have a negative impact on the Company's financial condition and ability to pursue its business strategies. If the Company is unable to obtain funding, the Company could be forced to delay, reduce or eliminate some or all of its research and development programs or commercialization efforts, which could adversely affect its business prospects.

The Company expects to seek additional funding in order to continue to fund its operations through public or private financing of debt or equity or collaboration agreements. Although management intends to pursue plans to obtain additional funding to finance its operations, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

The accompanying consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty. Accordingly, the consolidated financial statements have been prepared on a basis that assumes the Company will continue as a going concern and which contemplates the realization of assets and satisfaction of liabilities and commitments in the ordinary course of business.

## (2) Summary of Significant Accounting Policies

### *Use of Estimates*

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual for research and development expenses, the valuation of restricted ordinary shares and the valuation of share-based compensation awards. The Company bases its estimates on historical experience, known trends and other market-specific or other relevant factors that it believes to be reasonable under the circumstances. On an ongoing basis, management evaluates its estimates as there are changes in circumstances, facts and experience. Actual results could differ materially from those estimates.

### *Comprehensive Loss*

Comprehensive loss includes net loss as well as other changes in shareholders' equity that result from transactions and economic events other than those with shareholders. For the periods presented in the accompanying consolidated financial statements, there was no difference between net loss and comprehensive loss.

### *Consolidation*

The accompanying consolidated financial statements include the accounts of Iterum Therapeutics plc and its wholly owned subsidiaries (which are referred to herein, collectively, as the "Company" where context requires). All significant intercompany balances and transactions have been eliminated on consolidation. The Company has no involvement with variable interest entities.

### *Short-term investments*

The Company classifies short-term investments as available for sale in accordance with the terms of Financial Accounting Standards Board (FASB) Accounting Standard Codification (ASC) 320, *Investments – Debt and Equity Securities.* Realized gains and losses are determined using specific identification. The investments are reported at fair value, with unrealized gains or losses recorded in the consolidated statements of operations and comprehensive loss. Any difference between the cost and fair value of the investments are represented by unrealized gains or losses.

***Cash and Cash Equivalents***

The Company's cash and cash equivalents consist of cash balances and highly liquid investments with maturities of three months or less at the date of purchase. Accounts held at U.S. financial institutions are insured by the FDIC up to $250, while accounts held at Irish financial institutions are insured under the Deposit Guarantee Scheme up to $115 (€100).

Cash accounts with any type of restriction are classified as restricted cash. If restrictions are expected to be lifted in the next twelve months, the restricted cash account is classified as current. Included within restricted cash on the Company's consolidated balance sheet is a certificate of deposit for $120 which is being held by a third party bank as collateral for the irrevocable letter of credit issued in March 2018 to secure an office lease (see Note 11, Commitments and Contingencies).

***Foreign currencies***

Items included in the consolidated financial statements are measured using the currency of the primary economic environment in which the entity operates (functional currency). The consolidated financial statements are presented in U.S. dollars.

Transactions in foreign currencies are recorded at the rate of exchange at the date of the transaction. Monetary assets and liabilities denominated in foreign currencies at the balance sheet date are retranslated into the functional currency at the rate of exchange at the balance sheet date, and the resulting gains and losses are recognized in the consolidated statement of operations and comprehensive loss. Non-monetary items in a foreign currency that are measured in terms of historical cost are translated using the exchange rate at the date of transaction.

***Property and Equipment***

Property and equipment are stated at cost less accumulated depreciation. Property and equipment are depreciated using the straight-line method over the estimated useful life of each asset as follows:

| | Estimated Useful Life |
|---|---|
| Leasehold improvements | Shorter of life of lease or 10 years |
| Furniture and fixtures | 5 years |
| Laboratory equipment | 5 years |
| Computer equipment | 3 years |

Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is included in loss from operations. Repairs and maintenance costs are expensed as incurred. The Company reviews the recoverability of all long-lived assets, including the related useful life, whenever events or changes in circumstances indicate that the carrying amount of a long-lived asset might not be recoverable.

***Research and Development Expenses***

The Company expenses the cost of research and development as incurred. Research and development expenses comprise costs incurred in performing research and development activities, including salaries, share-based compensation and benefits, facilities costs, depreciation, manufacturing expenses and external costs of third-parties engaged to supply active pharmaceutical ingredient and drug product and conduct preclinical and clinical development activities and trials, as well as the cost of licensing technology, license fees, and other external costs. Advance payments for goods and services that will be used in future research and development activities are recorded as prepaid expenses and expensed when the activity is performed or when the goods have been received.

***Accrued Research and Development Expenses***

The Company has entered into various research and development contracts with research institutions and other companies. These agreements are generally cancelable, and related payments are recorded as research and development expenses as incurred. This process involves reviewing open contracts and purchase orders, communicating with Company personnel to identify services that have been performed on the Company's behalf and estimating the level of service performed and the associated cost incurred for the service when the Company has not yet been invoiced or otherwise notified of actual costs. The majority of the Company's service providers invoice in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. The Company estimates accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known at that time. It periodically confirms the accuracy of these estimates with the service providers and makes adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to:

- Vendors, including central laboratories, in connection with preclinical development activities;
- Clinical Research Organizations, or CROs, and investigative sites in connection with preclinical studies and clinical trials; and
- Contract Manufacturing Organizations, or CMOs, in connection with drug substance and drug product formulation of preclinical and clinical trial materials.

The Company bases expenses related to preclinical studies and clinical trials on estimates of the services received and efforts expended pursuant to quotes and contracts with multiple research institutions and CROs that conduct and manage preclinical studies and clinical trials on its 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 vendors will exceed the level of services provided and result in a prepayment of the expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing service fees, the Company estimates the time period over which services will be performed 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 the estimate, the accrual or the amount of prepaid expenses is adjusted accordingly. Although the Company does not expect the estimates to be materially different from amounts actually incurred, its understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. To date, there have not been any material adjustments to prior estimates of accrued research and development expenses.

***Patent Costs***

All patent related costs incurred in connection with filing and prosecuting patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses.

***Share-Based Compensation***

The Company measures all share-based awards granted to employees and directors based on the fair value on the date of grant using the Black-Scholes option-pricing model. Compensation expense of those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. The Company issues awards with service based vesting conditions only and records the expense for these awards using the straight-line method.

For awards granted to consultants and non-employees, compensation expense is recognized over the period during which services are rendered until completed. At the end of each financial reporting period prior to completion of the service, the fair value of these awards is remeasured using the then-current fair value of the Company's ordinary shares and updated assumption inputs in the Black-Scholes option-pricing model.

The Company classifies share-based compensation expense in its consolidated statement of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

The Black-Scholes option-pricing model uses key inputs and assumptions including the expected term of the option, share price volatility, risk-free interest rate, dividend yield, share price and exercise price. Many of the assumptions require significant judgment

and any changes could have a material impact in the determination of share-based compensation expense. The Company has elected to account for forfeitures as they occur.

***Grant Awards***

The Company may generate revenue from grant awards that reimburse certain allowable costs for specified projects. For contracts with third parties, when the Company has concluded that it is the principal in conducting the research and development, and where the funding arrangement is considered central to the Company's ongoing operations, it classifies the recognized funding received as revenue.

In June 2017, the Company was granted the CARB-X award in the amount of $1.5 million. The CARB-X award is structured as a cost reimbursement arrangement and is being recognized over a period of 20 months from August 2017.

The Company recognizes the CARB-X award as revenue, rather than as a reduction of research and development expenses, because the Company is the principal in conducting the research and development activities and this contract is central to its ongoing operations. Revenue is recognized as the qualifying expenses related to the contract are incurred. Five steps are applied in the revenue recognition process: (1) identify the contract with a customer; (2) identify the performance obligation in the contract; (3) determine the transaction price; (4) allocate the transaction price to the performance obligations in the contract; and (5) recognize revenue when (or as) the entity satisfies the performance obligation. Revenue recognized upon incurring qualifying expenses in advance of receipt of funding is recorded in the Company's consolidated balance sheet as other prepaid assets. The related costs incurred by the Company are included in research and development expenses in the Company's consolidated statements of operations and comprehensive loss. The Company recognized $869 and $508 as revenue for the years ended December 31, 2018 and 2017, respectively, in respect of the CARB-X Award. There was no revenue recognized for the year ended December 31, 2016.

***Research and Development Credits***

Research and development credits are available to the Company under the tax laws in Ireland, based on qualifying research and development spend as defined under those tax laws. Research and development credits are generally recognized as a reduction of research and development expenses.

***Fair Value of Financial Instruments***

FASB guidance specifies a hierarchy of valuation techniques based on whether the inputs to those valuation techniques are observable or unobservable. Observable inputs reflect market data obtained from independent sources, while unobservable inputs reflect market assumptions. The hierarchy gives the highest priority to unadjusted quoted prices in active markets for identical assets or liabilities (Level 1 measurement) and the lowest priority to unobservable inputs (Level 3 measurement).

The three levels of the fair value hierarchy are as follows:

- Level 1 — Unadjusted quoted prices in active markets for identical assets or liabilities that the reporting entity has the ability to access at the measurement date. Level 1 primarily consists of financial instruments whose value is based on quoted market prices such as exchange-traded instruments and listed equities.
- Level 2 — Inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly (e.g. quoted prices of similar assets or liabilities in active markets, or quoted prices for identical or similar assets or liabilities in markets that are not active). Level 2 includes financial instruments that are valued using models or other valuation methodologies.
- Level 3 — Unobservable inputs for the asset or liability. Financial instruments are considered Level 3 when their fair values are determined using pricing models, discounted cash flows or similar techniques and at least one significant model assumption or input is unobservable.

The Company's short-term investments and its advance payments to a supplier are carried at fair value, determined according to the fair value hierarchy above, see Note 3 for further details. The carrying amounts reported in the consolidated balance sheets for prepaid expenses and other current assets, accounts payable and accrued expenses approximate their fair value based on the short-term maturity of these instruments.

(In thousands, except share and per share data)

***Borrowings***

Interest bearing long-term debt is recognized initially at fair value, net of transactions costs incurred. Subsequent to initial recognition, interest bearing long-term debt is measured at amortized cost with any difference between cost and redemption value being recognized as a non-cash component of interest expense in the income statement over the period of the borrowings on an effective interest basis.

***Concentration of Credit Risk***

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and cash equivalents and short-term investments. The Company has most of its cash and cash equivalents and short-term investments at two accredited financial institutions in the United States, in amounts that exceed federally insured limits. The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

***Income Taxes***

The Company accounts for income taxes under the asset and liability method which requires deferred tax assets and liabilities to be recognized for the estimated future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases, as well as net operating loss carryforwards and research and development tax credits.

Valuation allowances are provided if it is more likely than not that some portion or all of the deferred tax assets will not be realized.

Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period that includes the enactment date. The Company recognizes the effect of income tax positions only if those positions are more likely than not of being sustained. Recognized income tax positions are measured at the largest amount that has a greater than 50% likelihood of being realized. Changes in recognition or measurement are reflected in the period in which the change in judgment occurs. The Company records interest related to unrecognized tax benefits in interest expense and penalties in general and administrative expenses.

On December 22, 2017, the United States federal government enacted the Tax Act, marking a change from a worldwide tax system to a modified territorial tax system in the United States. As part of this change, the Tax Act, among other changes, provided a reduction of the U.S. federal corporate income tax rate from 34% to 21%, an indefinite carryforward of net operating losses incurred in 2018 and future periods, and an interest limitation starting in 2018 with an indefinite carryforward. Any impact to the Company related to these items were accounted for in the 2017 and 2018 tax provisions with minimal impact.

***Net Loss Per Ordinary Share***

Basic and diluted net loss per ordinary share is determined by dividing net loss attributable to ordinary shareholders by the weighted-average ordinary shares outstanding during the period; in accordance with ASC 260, *Earnings per Share.* For the periods presented, the ordinary shares underlying the convertible preferred shares, options, unvested restricted ordinary shares, restricted share units and warrants have been excluded from the calculation because they would be anti-dilutive.

The following potentially dilutive securities have been excluded from the computation of diluted weighted-average shares outstanding as they would be anti-dilutive:

| | Year ended December 31, | | |
|---|---|---|---|
| | **2018** | **2017** | **2016** |
| Options to purchase ordinary shares | 665,219 | 248,128 | 49,330 |
| Preferred shares convertible into ordinary shares | — | 5,686,663 | 3,032,457 |
| Unvested restricted stock units | 36,924 | — | — |
| Unvested restricted ordinary shares | 86,068 | 189,342 | 292,620 |
| Warrants | 19,890 | — | — |
| **Total** | 808,101 | 6,124,133 | 3,374,407 |

(In thousands, except share and per share data)

The weighted-average shares outstanding used to calculate both basic and diluted loss per ordinary share are the same.

***Segment Information***

The Company determines and presents operating segments based on the information that is internally provided to the Chief Executive Officer, Chief Scientific Officer and Chief Financial Officer, who together are considered the Company's chief operating decision maker, in accordance with ASC 280, *Segment Reporting*. The Company has determined that it operates as a single business segment, which is the development and commercialization of innovative treatments for drug resistant bacterial infections.

The distribution of total operating expenses by geographical area was as follows:

| | Year ended December 31, | | |
|---|---|---|---|
| **Operating expenses** | **2018** | **2017** | **2016** |
| Ireland | $ 66,552 | $ 24,619 | $ 9,864 |
| U.S. | 10,876 | 5,344 | 3,495 |
| **Total** | $ 77,428 | $ 29,963 | $ 13,359 |

The distribution of long-lived assets by geographical area was as follows:

| **Long lived assets** | **December 31, 2018** | **December 31, 2017** |
|---|---|---|
| Ireland | $ 4,565 | $ 2,341 |
| U.S. | 245 | 243 |
| Total | $ 4,810 | $ 2,584 |

***Retirement Plan***

The Company has a defined contribution plan under Section 401(k) of the Internal Revenue Code (the '401(k) Plan'). The 401(k) Plan covers all U.S. employees who meet defined minimum age and service requirements, and allows participants to defer a portion of their annual compensation on a pre-tax basis. The Company is required to contribute a deferral rate of up to 3% to the 401(k) Plan on behalf of certain employees. The Company made contributions of $114 and $33 for the years ended December 31, 2018 and 2017, respectively.

***Inventory***

Inventories are valued at the lower of cost or net realizable value. Cost is determined using the first-in, first-out method for all inventories. The Company's policy is to write down inventory that has become obsolete, inventory that has a cost basis in excess of its expected net realizable value and inventory in excess of expected requirements. The estimate of excess quantities is subjective and primarily dependent on the estimates of future demand for a particular product. If the estimate of future demand changes, the Company considers the impact on the reserve for excess inventory and adjusts the reserve as required. Increases in the reserve are recorded as charges in cost of product sales. For product candidates that have not been approved by the U.S. Food and Drug Administration (FDA), inventory used in clinical trials is expensed at the time of production and recorded as research and development expenses. For products that have been approved by the FDA, inventory used in clinical trials is expensed at the time the inventory is packaged for the clinical trial. Prior to an advisory committee providing a recommendation to the FDA that the Company's application should be approved, costs related to manufacturing the product candidates are recorded as research and development expenses. All direct manufacturing costs incurred after this recommendation will be capitalized into inventory. The Company had no inventory as of December 31, 2018 or December 31, 2017.

***Contingent Consideration***

Certain license agreements contain milestone payments that could result in the requirement to make contingent consideration payments, see Note 11 for further details. Contingent consideration is recorded at the acquisition date estimated fair value of the contingent payment. The fair value of the contingent consideration is measured at each reporting period. Any related unwinding of discount is recognized as a finance expense. Other changes in fair value are recognized in profit or loss or capitalized as an intangible

(In thousands, except share and per share data)

asset depending on the stage of development. As of December 31, 2018, no milestones had been met that required the Company to recognize contingent consideration.

***Recent Accounting Pronouncements***

In July 2017, the FASB issued ASU 2017-11,*Earnings Per Share* (Topic 260), *Distinguishing Liabilities from Equity* (Topic 480), *Derivatives and Hedging* (Topic 815), I. Accounting for Certain Financial Instruments with Down Round Features, II. Replacement of the Indefinite Deferral for Mandatorily Redeemable Financial Instruments of Certain Nonpublic Entities and Certain Mandatorily Redeemable Noncontrolling Interests with a Scope Exception.

Part I applies to entities that issue financial instruments such as warrants, convertible debt or convertible preferred shares that contain down-round features. Part II replaces the indefinite deferral for certain mandatorily redeemable noncontrolling interests and mandatorily redeemable financial instruments of nonpublic entities contained within ASC Topic 480 with a scope exception and does not impact the accounting for these mandatorily redeemable instruments. ASU 2017-11 is required to be adopted for annual periods beginning after December 15, 2018, including interim periods within those fiscal years. The adoption of ASU 2017-11 is not expected to have a significant impact on the consolidated financial statements.

In February 2016, the FASB issued ASU 2016-02, *Leases* (Topic 842). ASU 2016-02 was issued to increase transparency and comparability among entities by recognizing lease assets and lease liabilities on the consolidated balance sheet and disclosing key information about lease arrangements. ASU 2016-02 is effective for public companies for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2018. In July 2018, the FASB issued ASU 2018-11 *Leases* (Topic 842): *Targeted Improvements* which provides the option to adopt the standard retrospectively for each prior period presented, as initially set out in ASU 2016-02, or as of the adoption date with a cumulative-effect adjustment to the opening balance of retained earnings. The updated standard is effective for us beginning in the first quarter of the year-ended December 31, 2019. We are currently evaluating the effect that the updated standard will have on our consolidated financial statements and related disclosures. See Note 11 Commitments and Contingencies for details of operating leases held as of December 31, 2018. A lease liability and right-of-use asset will be recorded on the consolidated balance sheet at December 31, 2019. We estimate the impact of the adoption of ASC 842 will be the recognition of a right-of use asset and of lease liabilities in the range of $7.6 million to $7.8 million. Under the new standard we expect an insignificant change in net result due to the replacement of operating leases expenses with amortization of the lease asset and the interest expense.

## (3) Fair Value of Financial Assets and Liabilities

The following table presents information about the Company's financial assets that were carried at fair value on a recurring basis on the consolidated balance sheet as of December 31, 2018 and December 31, 2017 and indicates the fair value hierarchy of the valuation inputs utilized to determine such fair value.

| **December 31, 2018** | | | | |
|---|---|---|---|---|
| **Assets** | **Total** | **Level 1** | **Level 2** | **Level 3** |
| Short-term investments | $ 40,000 | 40,000 | — | — |
| Other assets – advance payment to supplier | 2,649 | — | — | 2,649 |
| Total | $ 42,649 | 40,000 | — | 2,649 |

| **December 31, 2017** | | | | |
|---|---|---|---|---|
| **Assets** | **Total** | **Level 1** | **Level 2** | **Level 3** |
| Short-term investments | $ 30,731 | 30,731 | — | — |
| Other assets – advance payment to supplier | 1,472 | — | — | 1,472 |
| Total | $ 32,203 | 30,731 | — | 1,472 |

See Note 4 for further details on the short-term investments held. The other asset above relates to advance payments made to a supplier that were recorded at fair value using the discounted cash flow model, or DCF, as of December 31, 2018 and December 31, 2017. The fair value measurements of these advance payments were determined based on significant unobservable inputs, including a discount rate of 15% and the expected time to recovery of the payment. Changes to the inputs described above are not expected to have a material impact on the company's financial position and results of operations in any given period. See Note 11 — Payments to Supplier, for further details on these advance payments.

(In thousands, except share and per share data)

The following table presents information about the Company's long-term debt which was carried at amortized cost on the consolidated balance sheet as of December 31, 2018 and indicates the fair value hierarchy of the valuation inputs utilized to determine the approximate fair value. The Company did not hold any long-term debt as of December 31, 2017.

**December 31, 2018**

| Liabilities | Book Value | Approximate Fair Value | Level 1 | Level 2 | Level 3 |
|---|---|---|---|---|---|
| Current portion of long-term debt | $ 1,019 | $ 1,019 | | 1,019 | — |
| Long-term debt, less current portion | 13,079 | 13,035 | — | 13,035 | |
| Total | $ 14,098 | $ 14,054 | — | 14,054 | — |

The book value of the current portion of long-term debt approximates its fair value due to the short-term nature of the balance. The fair value of long-term debt, less current portion was determined based on a DCF analysis using quoted market interest rates, without consideration of transaction costs, which represents a Level 2 basis of fair value measurement. The counterparty to the long-term debt is a major international financial institution.

The carrying amounts reported in the consolidated balance sheets for prepaid expenses and other current assets, accounts payable and accrued expenses approximate their fair value based on the short-term maturity of these instruments.

There have been no transfers of assets or liabilities between the fair value measurement levels.

## (4) Short-term Investments

The Company classifies its short-term investments as available for sale. Short-term investments comprise highly liquid investments with minimum "A-" rated securities and as at period-end consist of U.S. Treasury and agency bonds and corporate entity commercial paper with maturities of more than three months but less than one year at the date of purchase. Short-term investments as of December 31, 2018 have an average maturity of 0.15 years. The investments are reported at fair value with unrealized gains or losses recorded in the consolidated statements of operations and comprehensive loss. Any differences between the cost and fair value of investments are represented by unrealized gains or losses. The fair value of short-term investments are represented by Level 1 fair value measurements – quoted prices in active markets for identical assets.

The following table represents the Company's available for sale short-term investments by major security type as of December 31, 2018 and December 31, 2017:

**December 31, 2018**

| | | | | | Maturity by period | |
|---|---|---|---|---|---|---|
| Available for sale | Cost Total | Unrealized gains | Unrealized (losses) | Fair Value Total | Less than 1 year | 1 to 5 years |
| Commercial paper | $ 35,745 | 272 | (9) | 36,008 | 36,008 | — |
| U.S. Treasury and Agency Bonds | 3,977 | 15 | — | 3,992 | 3,992 | — |
| Total | $ 39,722 | 287 | (9) | 40,000 | 40,000 | — |

**December 31, 2017**

| | | | | | Maturity by period | |
|---|---|---|---|---|---|---|
| Available for sale | Cost Total | Unrealized gains | Unrealized (losses) | Fair Value Total | Less than 1 year | 1 to 5 years |
| Commercial paper | $ 22,538 | 8 | (27) | 22,519 | 22,519 | — |
| U.S. Treasury and Agency Bonds | 8,205 | 18 | (11) | 8,212 | 8,212 | — |
| Total | $ 30,743 | 26 | (38) | 30,731 | 30,731 | — |

(In thousands, except share and per share data)

## (5) Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist of the following:

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| Prepaid research and development expenses | $ 5,351 | $ 2,289 |
| Short-term deposits | 959 | 1,346 |
| Other prepaid assets | 921 | 516 |
| Research and development tax credit receivable | 404 | 133 |
| Prepaid insurance | 438 | 117 |
| Value added tax receivable | 159 | 281 |
| Interest receivable | 158 | 95 |
| Deferred IPO expenses | — | 180 |
| Total | $ 8,390 | $ 4,957 |

## (6) Property and Equipment, net

Property and equipment and related accumulated depreciation are as follows:

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| Leasehold improvements | $ 592 | $ 579 |
| Furniture and fixtures | 120 | 108 |
| Laboratory equipment | 81 | 81 |
| Computer equipment | 108 | 44 |
| | 901 | 812 |
| Less: accumulated depreciation | (201) | (65) |
| | $ 700 | $ 747 |

Depreciation expense was $136 and $65 for the years ended December 31, 2018 and 2017, respectively. There was no depreciation expense for the year ended December 31, 2016.

## (7) Accrued Expenses

Accrued expenses consist of the following:

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| Accrued clinical trial costs | $ 2,849 | $ 594 |
| Accrued payroll and bonus expenses | 1,804 | 1,059 |
| Accrued manufacturing expenses | 1,439 | 2,031 |
| Accrued other expenses | 954 | 290 |
| Total | $ 7,046 | $ 3,974 |

## (8) Shareholders' Equity

The Company's capital structure consists of ordinary shares, undesignated preferred shares and, prior to the completion of the Company's IPO on May 30, 2018, convertible preferred shares with certain rights and privileges summarized below. Under Irish law, the Company is prohibited from allotting shares without consideration. Accordingly, at least the nominal value of the shares issued underlying any restricted share award, restricted share unit, performance share award, bonus share or any other share based grant must be paid pursuant to the Irish Companies Act.

***Ordinary Shares***

The Company was initially incorporated without a cap on its authorized share capital as permitted by the Companies Act 2014 of Ireland. On October 14, 2015, the Company authorized and issued 413,110 ordinary shares with a par value of $0.01 per share (after taking account of the reverse share split and redenomination of the par value of the ordinary shares from $0.01571 (the nominal value resulting from the reverse share split) to $0.01 on May 15, 2018). On March 13, 2018, the Company redenominated its 44,557,606 authorized and 413,110 issued ordinary shares from $0.0001 to $0.001 per share in accordance with section 83(1)(c) of the Companies Act 2014 in Ireland.

On November 18, 2015, the Company increased the authorized ordinary share capital to 3,659,453 shares with a par value of $0.01 per share.

On May 18, 2017, the Company increased the authorized ordinary share capital to 7,956,715 shares with a par value of $0.01 per share.

On February 16, 2018, the Company increased its authorized ordinary shares by 36,600,891 to 44,557,606 ordinary shares with a par value of $0.01 per share.

On May 30, 2018, the Company increased its authorized ordinary shares by 5,442,394 to 50,000,000 ordinary shares of $0.01 each.

On December 14, 2018, Iterum Therapeutics plc ("ITP") and Iterum Therapeutics International Limited ("ITIL") entered into a subscription agreement with a supplier of ITIL pursuant to which the supplier agreed to subscribe for ordinary shares in ITP in satisfaction of amounts due and owing under certain commercial agreements entered into between the supplier and ITIL (the "Subscription Agreement"). Pursuant to the terms of the Subscription Agreement, upon receipt by ITIL of a valid invoice from the supplier, ITP can elect to require the supplier to subscribe for ordinary shares in the capital of ITP (up to a maximum of 700,000 ordinary shares in total) to the value of the invoiced amount (a "Subscription"). On a Subscription, the supplier will direct ITIL to pay ITP such invoiced amount as subscription monies on the supplier's behalf in satisfaction of the invoiced amount.

On December 14, 2018, ITP elected that the supplier subscribe for 190,615 ordinary shares for an aggregate subscription price of $1.36 million (the "Subscription Monies") upon receipt by ITIL of valid invoices up to that amount from the supplier (the "Invoiced Amount"). On that date, ITP, ITIL and the supplier executed a payment direction letter pursuant to which the parties directed ITIL to pay $1.36 million (€1.20 million) to ITP in satisfaction of the supplier's obligation to pay the Subscription Monies to ITP and ITIL's obligation to pay the invoiced amount to the supplier.

The holders of ordinary shares are entitled to one vote for each share held. The holders of ordinary shares have no preemptive or other subscription rights, and there are no redemption or sinking fund provisions with respect to such shares.

***Undesignated Preferred Shares***

On May 30, 2018, the Company created a new class of undesignated preferred shares of $0.01 each, 100,000,000 of which were authorized immediately prior to closing of the initial public offering. The Directors are authorized by our Articles of Association to determine the rights attaching to the undesignated preferred shares including rights of redemption, rights as to dividends, rights on winding up and conversion rights. There were no undesignated preferred shares in issue as of December 31, 2018.

***Convertible Preferred Shares***

On November 18, 2015, the Company authorized 3,022,915 Series A convertible preferred shares with a par value of $0.01 per share. On the same day, the Company issued 1,514,320 Series A convertible preferred shares for a purchase price of $15.71 per share for: (1) gross cash proceeds of $20,701; (2) the issue of 190,961 convertible preferred shares to Pfizer as part consideration for the license agreement; and (3) the conversion of $90 debt owed by the Company to its founders for a total of 5,728 preferred shares (after taking account of the reverse share split and redenomination of the par value of the convertible preferred shares from $0.01571 (the nominal value resulting from the reverse share split) per share to $0.01 on May 15, 2018). On March 13, 2018, the Company redenominated its 3,032,463 authorized and 3,032,457 issued Series A convertible preferred shares from $0.0001 to $0.001 par value per share in accordance with section 83(1)(c) of the Companies Act 2014 in Ireland.

On December 9, 2016, the Company authorized 9,548 Series A convertible preferred shares with a par value of $0.01 per share.

On December 16, 2016, the Company issued 1,518,137 Series A convertible preferred shares for a purchase price of $15.71 per share for: (1) gross cash proceeds of $20,851; and (2) the issue of an additional 190,961 convertible preferred shares to Pfizer as part consideration for the license agreement.

On May 18, 2017, the Company authorized 2,654,215 Series B-1 convertible preferred shares with a par value of $0.01 per share and 1,042,728 Series B-2 convertible preferred shares with a par value of $0.01 per share (the "Series B convertible preferred shares"). On the same day, the Company issued 2,654,206 Series B-1 convertible preferred shares for a purchase price of $17.28 per share, for gross cash proceeds of $45,867 (after taking account of the reverse share split and redenomination of the par value of the convertible preferred shares from $0.01571 (the nominal value resulting from the reverse share split) per share to $0.01 on May 15, 2018). On March 13, 2018, the Company redenominated its 4,801,493 authorized and 4,363,856 issued Series B convertible preferred shares from $0.0001 to $0.001 par value per share in accordance with section 83(1)(c) of the Companies Act 2014 in Ireland.

On February 16, 2018, the Company increased its authorized Series B-2 convertible preferred shares to 2,147,278 shares with a par value of $0.01 per share. On the same day, the Company issued 1,709,650 Series B-2 convertible preferred shares for consideration of $18.85 per share, for gross cash proceeds of $32,230.

On May 30, 2018, immediately prior to the completion of the Company's IPO, holders of convertible preferred shares of Iterum Therapeutics Plc exchanged their preferred shares for ordinary shares of Iterum Therapeutics Plc on a one-for-one basis and all convertible preferred shares were subsequently cancelled.

Prior to the exchange and cancellation of preferred convertible shares on May 30, 2018, the ordinary shares were subordinate to the convertible preferred shares with respect to dividend rights and rights upon liquidation, winding up and dissolution of the Company and the holders of ordinary shares were entitled to liquidation proceeds after all liquidation preferences for the convertible preferred shares were satisfied.

**(9) Share-Based Compensation**

On November 18, 2015, the Company's Board of Directors adopted and approved the 2015 Equity Incentive Plan (the "2015 Plan"), which authorized the Company to grant up to 223,424 ordinary shares in the form of incentive share options, nonstatutory share options, share appreciation rights, restricted share awards, restricted share units and other share awards. The types of share-based awards, including the rights amount, terms, and exercisability provisions of grants are determined by the Company's Board of Directors. The purpose of the 2015 Plan is to provide the Company with the flexibility to issue share-based awards as part of an overall compensation package to attract and retain qualified personnel. On May 18, 2017, the Company amended the 2015 Plan to increase the number of ordinary shares available for issuance under the 2015 Plan by 219,605 shares to 443,029 shares.

On March 14, 2018, the Company's Board of Directors adopted and approved the 2018 Equity Incentive Plan (the "2018 Plan"), which became effective upon the execution and delivery of the underwriting agreement related to our IPO. No further grants will be made under the 2015 Plan. The ordinary shares underlying any options that are forfeited, cancelled, repurchased or are otherwise terminated by the Company under the 2015 Plan will not be added back to the ordinary shares available for issuance.

The 2018 Plan authorizes the Company to grant up to 1,018,459 ordinary shares in the form of incentive share options, nonstatutory share options, share appreciation rights, restricted share awards, restricted share units, performance share awards, performance cash awards and other share awards. The types of share-based awards, including the amount, terms, and exercisability provisions of grants are determined by the Company's Board of Directors. The ordinary shares underlying any options that are forfeited, cancelled, repurchased or are otherwise terminated by the Company under the 2018 Plan will be added back to the ordinary shares available for issuance under the 2018 Plan.

On December 5, 2018, pursuant to powers delegated to it by the Board of Directors of the Company, the Compensation Committee approved an increase in the number of ordinary shares available to be granted pursuant to the 2018 plan by 4% of the total number of shares of the Company's issued share capital on December 31, 2018, being 574,081 ordinary shares.

***Restricted Ordinary Shares***

In connection with the Company's formation, 413,110 restricted ordinary shares were issued on October 14, 2015 to the Company's founders at par value. These ordinary shares are subject to various restrictions pursuant to ordinary share purchase agreements between the Company and each founder, including restrictions on transfer and a Company right of repurchase. The

(In thousands, except share and per share data)

restricted ordinary shares were 25% vested as of October 14, 2016 and 1/36th of the remaining restricted ordinary shares vest on a monthly basis thereafter (subject to acceleration of vesting in connection with certain change of control transactions). A change in status occurred on November 18, 2015 when the founders became employees of the Company. The grant date of these shares is now considered to be November 18, 2015 when the fair value was $3.14 per share.

The Company records share-based compensation expense for the restricted ordinary shares based on the grant date fair value. The Company recorded an expense of $332 and $333 for the years ended December 31, 2018 and 2017, respectively. Total unamortized compensation expense related to restricted ordinary shares was $260 and $592 as of December 31, 2018 and December 31, 2017, respectively, expected to be recognized over a weighted average period of 0.79 years and 1.79 years as of December 31, 2018 and December 31, 2017, respectively.

A summary of the Company's restricted ordinary share activity and related information is as follows:

| | Number of Shares | Weighted Average Grant Date Fair Value per Share |
|---|---|---|
| Unvested at December 31, 2016 | 292,620 | $ 3.14 |
| Granted | — | |
| Vested | (103,278) | $ 3.14 |
| Forfeited | — | |
| Unvested at December 31, 2017 | 189,342 | $ 3.14 |
| Granted | — | |
| Vested | (103,274) | $ 3.14 |
| Forfeited | — | |
| Unvested at December 31, 2018 | 86,068 | $ 3.14 |

***Share Options***

Unless specified otherwise in an individual option agreement, share options granted under the 2015 Plan and the 2018 Plan generally have a ten year term and a four year vesting period. The vesting requirement is conditioned upon a grantee's continued service with the Company during the vesting period. Once vested, all awards are exercisable from the date of grant until they expire. The option grants are non-transferable. Vested options generally remain exercisable for 90 days subsequent to the termination of the option holder's service with the Company. In the event of an option holder's disability or death while employed by or providing service to the Company, the exercisable period extends to twelve months or eighteen months, respectively.

The fair value of options granted during the years ended December 31, 2018 and 2017 was estimated using the Black-Scholes option-pricing model. The inputs for the Black-Scholes model require management's significant assumptions. The risk-free interest rate was based on a normalized estimate of the 7-year U.S. treasury yield. The Company has estimated the expected term utilizing the "simplified" method for awards that qualify as "plain vanilla". The Company does not have sufficient company-specific historical and implied volatility information and it therefore estimates its expected share volatility based on historical volatility information of reasonably comparable guideline public companies. The Company expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded share price. Expected dividend yield is based on the fact that the Company has never paid cash dividends, its ability to pay cash dividends is currently prohibited by the terms of its credit facility with SVB and the Company's future ability to pay cash dividends on its shares may be limited by the terms of any future debt or preferred securities.

The Company granted 479,986 and 198,798 share options to employees and directors during the years ended December 31, 2018 and 2017, respectively. There were 566,813 and 228,809 unvested employee and director options outstanding as of December 31, 2018 and December 31, 2017, respectively. Total expense recognized related to the employee and director share options was $669 and $59 for the years ended December 31, 2018 and 2017, respectively. Total unamortized compensation expense related to employee and director share options was $2,822 and $396 as of December 31, 2018 and December 31, 2017, respectively, which is expected to be recognized over a remaining average vesting period of 3.07 years and 3.51 years as of December 31, 2018 and December 31, 2017, respectively.

The assumptions that the Company used to determine the grant date fair value of employee and director options granted were as follows, presented on a weighted average basis:

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | 2016 |
| Volatility | 60% | 60% | 60% |
| Expected term in years | 1 - 6.25 | 6.25 | 6.25 |
| Dividend rate | 0% | 0% | 0% |
| Risk-free interest rate | 2.16 - 2.91% | 1.63% | 2.00% |

The following table summarizes the number of options outstanding and the weighted-average exercise price:

| | Number of Shares | Weighted Average Exercise Price | Weighted Average Remaining Contractual Life in Years | Aggregate Intrinsic Value (in thousands) |
|---|---|---|---|---|
| Options outstanding December 31, 2016 | 49,330 | $ 3.14 | 8.51 | |
| Granted | 198,798 | $ 3.36 | 9.67 | |
| Exercised | — | | | |
| Forfeited | — | | | |
| Options outstanding December 31, 2017 | 248,128 | $ 3.31 | 9.44 | |
| Granted | 479,986 | $ 12.60 | 9.45 | |
| Exercised | (2,008) | $ 3.30 | | 8 |
| Forfeited | (60,887) | $ 10.99 | | |
| Options outstanding December 31, 2018 | 665,219 | $ 9.31 | 8.93 | 395 |
| Exercisable at December 31, 2018 | 98,406 | $ 3.71 | 7.20 | 162 |

The aggregate intrinsic value of share options is calculated as the difference between the exercise price of the share options and the fair value of the Company's ordinary shares for those share options that had exercise prices lower than the fair value of the Company's ordinary shares at December 31, 2018.

The weighted average grant-date fair value per share of share options granted during the years ended December 31, 2018, 2017 and 2016 was $7.25, $1.91 and $1.80, respectively.

(In thousands, except share and per share data)

***Restricted Share Units (RSUs)***

The Company granted 36,924 restricted share units to directors during the year ended December 31, 2018. The restricted share units granted have a one year vesting period conditional upon the directors continued service with the Company during the vesting period. All restricted share units granted were unvested as of December 31, 2018. Total expense recognized related to the restricted share units was $289 for the year ended December 31, 2018. Total unamortized compensation expenses related to restricted share units was $191 as of December 31, 2018 which is expected to be recognized over a remaining average vesting period of 0.40 years as of December 31, 2018.

There were no restricted share units granted prior to the year ended December 31, 2018.

A summary of the Company's restricted share unit activity and related information is as follows:

| | Number of Shares | Weighted Average Grant Date Fair Value per Share |
|---|---|---|
| RSUs outstanding December 31, 2017 | — | |
| Granted | 36,924 | $ 13.00 |
| Shares vested | — | |
| Forfeited | — | |
| RSUs outstanding December 31, 2018 | 36,924 | $ 13.00 |

The Company's share-based compensation expense was classified in the consolidated statements of operations and comprehensive loss as follows:

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | 2016 |
| Research and development expense | $ 398 | $ 139 | $ 115 |
| General and administrative expense | 892 | 253 | 233 |

There was a total of $3,273 and $988 unamortized share-based compensation expense for restricted ordinary shares, options and restricted share units as of December 31, 2018 and December 31, 2017, respectively, which is expected to be recognized over a remaining average vesting period of 2.71 years and 2.53 years as of December 31, 2018 and December 31, 2017, respectively.

## (10) Income Taxes

During the years ended December 31, 2018, 2017 and 2016, the Company recorded no income tax benefits for the net operating losses incurred in each year due to its uncertainty of realizing a benefit from those items.

The provision for income taxes consists of the following components:

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | 2016 |
| Current | | | |
| Ireland | $ 472 | $ 444 | $ 113 |
| U.S. | — | — | — |
| Total Current | $ 472 | $ 444 | $ 113 |
| | | | |
| Deferred | | | |
| Ireland | $ — | $ — | $ — |
| U.S. | — | — | — |
| Total Deferred | $ — | $ — | $ — |
| Income Tax Provision | $ 472 | $ 444 | $ 113 |

(In thousands, except share and per share data)

Income taxes have been based on the following components of income (loss) before provision for income taxes:

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | 2016 |
| Ireland | $ 532 | $ 875 | $ (50) |
| U.S. | $ (77,116) | (29,837) | (13,301) |
| Total | $ (76,584) | $ (28,962) | $ (13,351) |

The Irish federal statutory rate is reconciled to the effective tax rate as follows:

| | Year ended December 31, 2018 | | Year ended December 31, 2017 | | Year ended December 31, 2016 | |
|---|---|---|---|---|---|---|
| Statutory rate | 12.50% | $ (9,573) | 12.50% | $ (3,620) | 12.50% | $ (1,669) |
| Impact of U.S. tax rate | (0.11)% | 81 | (0.80)% | 232 | 0.10% | (13) |
| Impact of valuation allowance | (11.42)% | 8,749 | (13.64)% | 3,949 | (12.80)% | 1,708 |
| Research and development tax credit | 0.45% | (341) | 0.76% | (220) | — | — |
| Other, net | (2.03)% | 1,557 | (0.36)% | 103 | (0.65)% | 87 |
| Effective tax rate | (0.61)% | $ 472 | (1.54)% | $ 444 | (0.85)% | $ 113 |

The significant components of the Company's deferred tax assets and liabilities are as follows:

| | Year ended December 31, | | |
|---|---|---|---|
| | 2018 | 2017 | 2016 |
| Deferred tax assets | | | |
| Share-based compensation | $ 27 | $ 3 | $ 1 |
| Depreciation | (49) | 6 | — |
| Net operating loss carryforwards | 13,648 | 5,409 | 1,706 |
| 163(j) interest expense limitation | 115 | — | — |
| Other | 665 | 239 | 1 |
| Valuation allowance | (14,406) | (5,657) | (1,708) |
| Total deferred tax assets | $ — | $ — | $ — |
| | | | |
| Deferred tax liabilities | | | |
| | — | — | — |
| Total deferred tax assets | $ — | $ — | $ — |
| | | | |
| Net deferred tax asset | $ — | $ — | $ — |

As a Company incorporated in Ireland, it is principally subject to taxation in Ireland.

The Company has net operating loss carryforwards in Ireland which result in tax benefits of approximately $13,648, $5,409 and $1,706 as of the years ended December 31, 2018, 2017 and 2016, respectively, for which a full valuation allowance has been recognized as it was determined that it is more-likely-than-not that these net deferred tax assets will not be realized. The net operating loss carryforwards do not expire, but are carried forward indefinitely. Realization of these deferred tax assets is dependent on the generation of sufficient taxable income. If the Company demonstrates consistent profitability in the future, the evaluation of the recoverability of these deferred tax assets may change and the remaining valuation allowance may be released in part or in whole. While management expects to realize the deferred tax assets, net of valuation allowances, changes in estimates of future taxable income or in tax laws may alter this expectation.

On December 22, 2017, the United States federal government enacted the Tax Act, marking a change from a worldwide tax system to a modified territorial tax system in the United States. As part of this change, the Tax Act, among other changes, provided a reduction of the U.S. federal corporate income tax rate from 34% to 21%, an indefinite carryforward of net operating losses incurred in 2018 and future periods, and an interest limitation starting in 2018 with an indefinite carryforward. Any impact to the Company related to these items were accounted for in the 2017 and 2018 tax provisions with minimal impact.

(In thousands, except share and per share data)

A reconciliation of the beginning and ending amount of gross unrecognized tax benefits is as follows:

| | 2018 | 2017 |
|---|---|---|
| Balance at January 1 | $ 30 | $ — |
| Additions | $ 398 | 30 |
| Balance at December 31 | $ 428 | $ 30 |

The Company is generally subject to examination in the Company's primary tax jurisdictions for tax years beginning 2015. The Company is not currently subject to any audits or examination.

## (11) Commitments and Contingencies

***Operating Leases***

In June 2018, the Company entered into an operating lease agreement for a commercial unit in Dublin for a period of 20 years with a 10 year break option, that commenced in June 2018. Annual lease payments are $315, subject to certain escalations at each five year interval. Under the terms of the lease, the Company provided a security deposit of $802 to the landlord, which is included in other assets in the accompanying balance sheet.

In March 2018, the Company entered into an operating lease agreement for office space in Chicago for a period of five years that commenced in June 2018. Annual lease payments are $258, subject to certain escalations, with a renewal option to extend the lease for an additional five years. Under the terms of the lease, the Company provided a security deposit in the form of a letter of credit for the benefit of the landlord in the amount of $120 which amount will be reduced incrementally over the term of the lease. The letter of credit outstanding is collateralized with a certificate of deposit.

In April 2017, the Company entered into an operating lease agreement for office space in Connecticut for a period of five years that commenced in July 2017. Annual lease payments are $131, subject to certain escalations, with a renewal option to extend the lease for an additional three years. Under the terms of the lease, the Company provided a security deposit of $17 to the landlord, which is included in other assets in the accompanying consolidated balance sheets.

In December 2016, the Company entered into an operating lease agreement for office space in Dublin for a period of ten years that commenced on December 1, 2016. The lease requires annual payments of $331 over the ten-year term with a renewal option to extend the lease for an additional five years. Under the terms of the lease, the Company provided a security deposit of $331 to the landlord, which is included in other assets in the accompanying consolidated balance sheets. The lease is subject to a review in December 2022.

The following table summarizes the future minimum payments due under the operating leases as of December 31, 2018:

| Year Ending December 31, | |
|---|---|
| 2019 | 904 |
| 2020 | 1,020 |
| 2021 | 1,030 |
| 2022 | 985 |
| 2023 | 766 |
| Thereafter | 2,356 |
| | $ 7,061 |

***License Agreement***

On November 18, 2015, the Company entered into a license agreement with Pfizer for the worldwide exclusive rights to research, develop, manufacture and commercialize sulopenem.

As part of the license agreement, the Company is obligated to pay Pfizer potential future regulatory milestone payments, as well as sales milestones upon achievement of net sales ranging from $250.0 million to $1.0 billion for each product type. The Company is

also obligated to pay Pfizer royalties ranging from a single-digit to mid-teens percentage based on marginal net sales of each licensed product.

***Payments to Supplier***

In June 2016, the Company entered into an agreement with a supplier whereby the Company would pay $2,864 to the supplier to acquire equipment which will be used solely to manufacture product for the Company. In June 2018, the Company entered into a supplemental agreement with this supplier whereby the Company would pay an additional $2,348 under the same terms as the original agreement. These payments will be offset against the price of the product to be supplied under a future supply agreement. $1,604 and $599 remained outstanding to the supplier as of December 31, 2018 and December 31, 2017, respectively.

***Contingencies***

Liabilities for loss contingencies arising from claims, assessments, litigation, fines, penalties and other sources are recorded when it is probable that a liability has been incurred and the amount can be reasonably estimated. At each reporting date the Company evaluates whether or not a potential loss amount or a potential loss range is probable and reasonably estimable under the provisions of the authoritative guidelines that address accounting for contingencies. The Company expenses costs as incurred in relation to such legal proceedings. The Company is not currently involved in any legal matters arising in the normal course of business.

Under the terms of their respective employment agreements, each of the executive officers is eligible to receive severance payments and benefits upon a termination without “cause” or due to “permanent disability”, or upon “resignation for good reason”, contingent upon the named executive officer’s continued performance for the Company.

**(12) Debt**

On April 27, 2018, the Company’s subsidiaries, Iterum Therapeutics International Limited, Iterum Therapeutics US Holding Limited and Iterum Therapeutics US Limited, entered into a Loan and Security Agreement with SVB and made an initial draw of $15,000 on closing. A second draw of up to $15,000 will be available to the Company through October 31, 2019, upon satisfaction of either (i) the achievement by the Company of both non-inferiority and superiority primary endpoints from its Phase 3 uncomplicated urinary tract infection (uUTI) trial, as well as reporting satisfactory safety data from the trial, or (ii) the achievement of non-inferiority primary endpoints from both its Phase 3 uUTI and complicated urinary tract infection (cUTI) trials, as well as reporting satisfactory safety data from the trials. The Company’s option to draw the second term loan will terminate upon the earliest to occur of October 31, 2019, the thirtieth day following the occurrence of either of the foregoing conditions, or the occurrence of an event of default.

The initial draw requires monthly amortization payments commencing on November 1, 2019; however this will extend to April 1, 2020 if the second draw is funded. Interest will accrue at a floating per annum rate equal to the greater of (i) 8.31%; or (ii) 3.89% above the Wall Street Journal prime rate, and is payable monthly in arrears. All outstanding principal, plus a 4.20% final interest payment, will be due and payable on the earliest to occur of March 1, 2022 (the maturity date), the acceleration of either term loan or the prepayment of either term loan. The final payment fee of $0.6 million, which represents 4.2% of the funded loan, is accreted using the effective interest method over the life of the loan as interest expense. Voluntary prepayments will be permitted at any time, subject to a prepayment fee of 3.00% in the first year, 2.00% in the second year, and 1.00% thereafter.

In connection with the initial $15,000 draw, the Company issued SVB and Life Sciences Fund II LLC (LSF) warrants to purchase an aggregate of 19,890 Series B convertible preferred shares (which converted into warrants to purchase 19,890 ordinary shares upon the Company’s IPO) at an exercise price of $18.85 per share. On the funding date of the second term loan, each of SVB and LSF will be automatically entitled to purchase additional ordinary shares in an aggregate amount equal to 2.50% of the second term loan divided by the applicable exercise price.

The loan proceeds were allocated based on the relative fair values of the debt instrument and the warrant instrument. The fair value of the warrants and the closing costs were recorded as debt discounts and are being amortized using the effective interest rate method over the term of the loan. The effective annual interest rate of the outstanding debt is approximately 12.03% as of December 20, 2018. For the year ended December 31, 2018, the Company recognized $1,169 of interest expense related to the loan agreement, including $360 related to the accretion of the debt discounts and deferred financing costs.

(In thousands, except share and per share data)

Scheduled principal payments on outstanding debt, as of December 31, 2018, are as follows:

| Year Ending December 31, | |
|---|---|
| 2019 | 1,034 |
| 2020 | 6,207 |
| 2021 | 6,207 |
| 2022 | 1,552 |
| | $ 15,000 |

## (13) Quarterly Financial Data (unaudited)

| | Three months ended | | | |
|---|---|---|---|---|
| | December 31, 2018 | September 30, 2018 | June 30, 2018 | March 31, 2018 |
| Revenue | $ 239 | $ 254 | $ 185 | $ 191 |
| Total operating expenses | (24,183) | (25,240) | (15,611) | (12,394) |
| Net loss and comprehensive loss | (24,258) | (24,905) | (15,747) | (12,146) |
| Net loss attributable to ordinary shareholders | (24,258) | (24,905) | (15,747) | (12,146) |
| Net loss per share attributable to ordinary shareholders – basic and diluted | $ (1.72) | $ (1.77) | $ (2.22) | $ (61.36) |
| Weighted average ordinary shares outstanding – basic and diluted | 14,108,604 | 14,034,631 | 7,085,655 | 197,949 |

| | Three months ended | | | |
|---|---|---|---|---|
| | December 31, 2017 | September 30, 2017 | June 30, 2017 | March 31, 2017 |
| Revenue | $ 349 | $ 159 | $ — | $ — |
| Total operating expenses | (9,553) | (8,455) | (6,413) | (5,542) |
| Net loss and comprehensive loss | (9,118) | (8,171) | (6,280) | (5,837) |
| Net loss attributable to ordinary shareholders | (9,118) | (8,171) | (6,280) | (5,837) |
| Net loss per share attributable to ordinary shareholders – basic and diluted | $ (43.24) | $ (44.16) | $ (39.44) | $ (103.68) |
| Weighted average ordinary shares outstanding – basic and diluted | 210,859 | 185,040 | 159,221 | 56,301 |

## (14) Subsequent Events

There have been no events subsequent to the year-end which would require adjustment to, or disclosure in, the Annual Report on Form 10-K.

**Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure.**

None.

**Item 9A. Controls and Procedures.**

***Evaluation of Disclosure Controls and Procedures***

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer (our principal executive officer and principal financial officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2018. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate, to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2018, our Chief Executive Officer and Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

***Management's Annual Report on Internal Controls Over Financial Reporting***

This Annual Report on Form 10-K does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our independent registered public accounting firm due to a transition period established by rules of the SEC for newly public companies.

***Changes in Internal Control over Financial Reporting***

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the year ended December 31, 2018, that has materially affected, or is 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 is incorporated herein by reference to our definitive Proxy Statement to be filed in connection with our 2019 Annual General Meeting of Shareholders, or our 2019 Proxy Statement, which will be filed with the Securities and Exchange Commission within 120 days after December 31, 2018.

We have adopted a written Code of Business Conduct and Ethics that applies to all officers, directors and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. The Code of Business Conduct and Ethics is available on our website at www.iterumtx.com. If we make any substantive amendments to the Code of Business Conduct and Ethics or grant any waiver from a provision of the Code of Business Conduct and Ethics to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on our website or in a Current Report on Form 8-K.

### Item 11. Executive Compensation.

The information required by this item is incorporated herein by reference to our 2019 Proxy Statement

### Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Shareholder Matters.

The information required by this item is incorporated herein by reference to our 2019 Proxy Statement.

### Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this item is incorporated herein by reference to our 2019 Proxy Statement.

### Item 14. Principal Accounting Fees and Services.

The information required by this item is incorporated herein by reference to our 2019 Proxy Statement.

## PART IV

**Item 15. Exhibits, Financial Statement Schedules.**

**(1) Consolidated Financial Statements**

See Index to Consolidated Financial Statements at Item 8 herein.

**(2) Financial Statement Schedules**

All schedules are omitted because they are not applicable or the required information is shown in the consolidated financial statements or notes thereto.

**(3) Exhibits**

The following is a list of exhibits filed or furnished as part of this Annual Report on Form 10-K;

| Exhibit No. | Description of Document | Filed with this report | Incorporated by Reference herein from Form or Schedule | Filing Date | SEC File Number |
|---|---|---|---|---|---|
| 3.1 | Constitution of Iterum Therapeutics plc | | Form 8-K (Exhibit 3.1) | 5/30/2018 | 001-38503 |
| 4.1 | Form of Ordinary Share Certificate of Registrant. | | Form S-1 (Exhibit 4.1) | 5/1/2018 | 333-224582 |
| 10.1† | License Agreement by and among Registrant, Iterum Therapeutics International Limited and Pfizer Inc. dated as of November 18, 2015. | | Form S-1 (Exhibit 10.1) | 5/1/2018 | 333-224582 |
| 10.2 | Amended and Restated Investor Rights Agreement by and between Registrant and certain of its shareholders dated May 18, 2017. | | Form S-1 (Exhibit 10.2) | 5/1/2018 | 333-224582 |
| 10.3+ | 2015 Equity Incentive Plan. | | Form S-1 (Exhibit 10.3) | 5/1/2018 | 333-224582 |
| 10.4+ | Forms of U.S. Stock Option Agreement, Stock Option Grant Notice and Notice of Exercise under the 2015 Equity Incentive Plan. | | Form S-1 (Exhibit 10.4) | 5/1/2018 | 333-224582 |
| 10.5+ | Forms of Irish Stock Option Agreement, Stock Option Grant Notice and Notice of Exercise under the 2015 Equity Incentive Plan. | | Form S-1 (Exhibit 10.5) | 5/1/2018 | 333-224582 |
| 10.6+ | 2018 Equity Incentive Plan. | | Form S-1/A (Exhibit 10.6) | 5/16/2018 | 333-224582 |
| 10.7+ | Forms of U.S. Stock Option Terms and Conditions and Stock Option Grant Notice under the 2018 Equity Incentive Plan. | | Form S-1 (Exhibit 10.7) | 5/1/2018 | 333-224582 |
| 10.8+ | Forms of International Stock Option Terms and Conditions and Stock Option Grant Notice under the 2018 Equity Incentive Plan. | | Form S-1 (Exhibit 10.8) | 5/1/2018 | 333-224582 |
| 10.9+ | Form of Restricted Share Unit Award Agreement under the 2018 Equity Incentive Plan. | | Form S-1 (Exhibit 10.9) | 5/1/2018 | 333-224582 |
| 10.1 | Form of Indemnity Agreement by and between the Registrant and its directors and officers. | | Form S-1 (Exhibit 10.10) | 5/1/2018 | 333-224582 |
| 10.11 | Form of Indemnity Agreement by and between Iterum Therapeutics US Limited and its directors and officers. | | Form S-1 (Exhibit 10.11) | 5/1/2018 | 333-224582 |
| 10.12+ | Employment Terms by and between Iterum Therapeutics US Limited and Corey N. Fishman dated November 18, 2015. | | Form S-1 (Exhibit 10.12) | 5/1/2018 | 333-224582 |
| 10.13+ | Amendment to Employment Agreement by and between Iterum Therapeutics US Limited and Corey N. Fishman dated May 2, 2018. | | Form S-1/A (Exhibit 10.13) | 5/4/2018 | 333-224582 |
| 10.14+ | Employment Terms by and between Iterum Therapeutics US Limited and Michael W. Dunne dated November 18, 2015. | | Form S-1 (Exhibit 10.14) | 5/1/2018 | 333-224582 |
| 10.15+ | Employment Terms by and between Iterum Therapeutics US Limited and Judith M. Matthews dated November 18, 2015. | | Form S-1 (Exhibit 10.15) | 5/1/2018 | 333-224582 |
| 10.16+ | Amendment to Employment Agreement by and between Iterum Therapeutics US Limited and Judith M. Matthews dated May 2, 2018. | | Form S-1/A (Exhibit 10.16) | 5/4/2018 | 333-224582 |
| 10.17+ | Employment Terms by and between Iterum Therapeutics US Limited and Jeffrey Schaffnit dated February 9, 2018. | | Form S-1 (Exhibit 10.17) | 5/1/2018 | 333-224582 |
| 10.18+ | Non-Employee Director Compensation Policy. | | Form S-1/A (Exhibit 10.18) | 5/16/2018 | 333-224582 |

| Exhibit No. | Description of Document | Filed with this report | Incorporated by Reference herein from Form or Schedule | Filing Date | SEC File / Registration Number |
|---|---|---|---|---|---|
| 10.19 | Loan and Security Agreement by and among Silicon Valley Bank, Iterum Therapeutics International Limited, Iterum Therapeutics US Holding Limited, and Iterum Therapeutics US Limited, dated April 27, 2018. | | Form S-1/A (Exhibit 10.19) | 5/4/2018 | 333-224582 |
| 10.2 | Intellectual Property Security Agreement by and among Silicon Valley Bank, the Registrant, Iterum Therapeutics International Limited, Iterum Therapeutics US Holding Limited, and Iterum Therapeutics US Limited, dated April 27, 2018. | | Form S-1/A (Exhibit 10.20) | 5/4/2018 | 333-224582 |
| 10.21 | Warrant to Subscribe for Shares, issued to Silicon Valley Bank, dated April 27, 2018. | | Form S-1/A (Exhibit 10.21) | 5/4/2018 | 333-224582 |
| 10.22 | Warrant to Subscribe for Shares, issued to Life Sciences Fund II LLC, dated April 27, 2018. | | Form S-1/A (Exhibit 10.22) | 5/4/2018 | 333-224582 |
| 10.23 | Additional Form of Warrant to Subscribe for Ordinary Shares as may be issued to Silicon Valley Bank pursuant to the Loan and Security Agreement. | | Form S-1/A (Exhibit 10.23) | 5/4/2018 | 333-224582 |
| 10.24 | Additional Form of Warrant to Subscribe for Ordinary Shares as may be issued to Life Sciences Fund II LLC pursuant to the Loan and Security Agreement. | | Form S-1/A (Exhibit 10.24) | 5/4/2018 | 333-224582 |
| 21.1 | Subsidiaries of the Registrant. | X | | | |
| 23.1 | Consent of KPMG, Independent Registered Public Accounting Firm. | X | | | |
| 31.1 | Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. | X | | | |
| 31.2 | Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002. | X | | | |
| 32.1 | Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. | X | | | |
| 32.2 | Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. | X | | | |
| 101.INS | XBRL Instance Document | X | | | |
| 101.SCH | XBRL Taxonomy Extension Schema Document | X | | | |
| 101.CAL | XBRL Taxonomy Extension Calculation Linkbase Document | X | | | |
| 101.DEF | XBRL Taxonomy Extension Definition Linkbase Document | X | | | |
| 101.LAB | XBRL Taxonomy Extension Label Linkbase Document | X | | | |
| 101.PRE | XBRL Taxonomy Extension Presentation Linkbase Document | X | | | |

+ Indicates management contract or compensatory plan.

† Confidential treatment has been requested for certain provisions omitted from this Exhibit pursuant to Rule 406 promulgated under the Securities Act. The omitted information has been filed separately with the Securities and Exchange Commission.

**Item 16. Form 10-K Summary**

None.

**SIGNATURES**

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

ITERUM THERAPEUTICS PLC

Date: March 25, 2019

By: /s/ Corey N. Fishman
Corey N. Fishman
President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

| SIGNATURE | TITLE | DATE |
|---|---|---|
| /s/ Corey N. Fishman<br>Corey N. Fishman | President and Chief Executive Officer (Principal Executive Officer) | March 25, 2019 |
| /s/ Judith M. Matthews<br>Judith M. Matthews | Chief Financial Officer (Principal Financial and Accounting Officer) | March 25, 2019 |
| /s/ Paul R. Edick<br>Paul R. Edick | Chairman of the Board of Directors | March 25, 2019 |
| /s/ Brenton K. Ahrens<br>Brenton K. Ahrens | Director | March 25, 2019 |
| /s/ Mark Chin<br>Mark Chin | Director | March 25, 2019 |
| /s/ James I. Healy<br>James I. Healy, M.D., Ph.D. | Director | March 25, 2019 |
| /s/ Patrick J. Heron<br>Patrick J. Heron | Director | March 25, 2019 |
| /s/ Ronald M. Hunt<br>Ronald M. Hunt | Director | March 25, 2019 |
| /s/ David G. Kelly<br>David G. Kelly | Director | March 25, 2019 |
| /s/ Shahzad Malik<br>Shahzad Malik, M.D. | Director | March 25, 2019 |

**Exhibit 21.1**

**LIST OF SUBSIDIARIES OF ITERUM THERAPEUTICS PLC**

| Subsidiary | Jurisdiction |
|---|---|
| Iterum Therapeutics International Limited | Ireland |
| Iterum Therapeutics US Limited | Delaware |
| Iterum Therapeutics US Holding Limited | Delaware |

**Exhibit 23.1**

**CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

The Shareholders and Board of Directors
Iterum Therapeutics plc:

We consent to the incorporation by reference in the registration statement (No. 333-225236) on Form S-8 of Iterum Therapeutics plc of our report dated March 25, 2019, with respect to the consolidated balance sheets of Iterum Therapeutics plc as of December 31, 2018 and 2017, the related consolidated statements of operations and comprehensive loss, convertible preferred shares and shareholders' equity, and cash flows for each of the years in the three-year period ended December 31, 2018, and the related notes, which report appears in the December 31, 2018 annual report on Form 10-K of Iterum Therapeutics plc.

/s/ KPMG

Dublin, Ireland
March 25, 2019

**Exhibit 31.1**

**CERTIFICATION PURSUANT TO**
**RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,**
**AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Corey Fishman, certify that:

1. I have reviewed this Annual Report on Form 10-K of Iterum Therapeutics plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 25, 2019

By: /s/ Corey Fishman

**Corey Fishman**
**President and Chief Executive Officer**
**(Principal Executive Officer)**

**Exhibit 31.2**

**CERTIFICATION PURSUANT TO**
**RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,**
**AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002**

I, Judith Matthews, certify that:

1. I have reviewed this Annual Report on Form 10-K of Iterum Therapeutics plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 25, 2019

By: /s/ Judith Matthews

**Judith Matthews**
**Chief Financial Officer**
**(Principal Financial and Accounting Officer)**

**Exhibit 32.1**

**CERTIFICATION PURSUANT TO**
**18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO**
**SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report on Form 10-K of Iterum Therapeutics plc (the "Company") for the year ended December 31, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Corey Fishman, President and Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to his knowledge on the date hereof:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 25, 2019

By: /s/ Corey Fishman

**Corey Fishman**
**President and Chief Executive Officer**
**(Principal Executive Officer)**

**Exhibit 32.2**

**CERTIFICATION PURSUANT TO**
**18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO**
**SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report on Form 10-K of Iterum Therapeutics plc (the "Company") for the year ended December 31, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Judith Mathews, Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to her knowledge on the date hereof:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 25, 2019

By: /s/ Judith Matthews

**Judith Matthews**
**Chief Financial Officer**
**(Principal Financial and Accounting Officer)**