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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, 2021

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: 001-38670

Entasis Therapeutics Holdings Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**82-4592913**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

35 Gatehouse Drive
Waltham, MA 02451
(781) 810-0120
(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

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

Title of each class:	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.001 per share	**ETTX**	**Nasdaq Global Market**

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

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

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Securities 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 the filing requirements for the past 90 days. Yes ☒ No ☐

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. (Check one):

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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

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

As of June 30, 2021, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of shares of the registrant's common stock held by non-affiliates of the registrant was approximately $28.6 million, based on the closing price of the registrant's common stock on The Nasdaq Global Market on June 30, 2021 of $2.67 per share. The calculation excludes shares of the registrant's common stock held by current executive officers, directors and stockholders that the registrant has concluded are affiliates of the registrant. The determination of affiliate status is not a determination for other purposes.

As of February 25, 2022, there were 47,851,779 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Specified portions of the registrant's definitive proxy statement for its 2021 Annual Meeting of Stockholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2020, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or Exchange Act, and the Private Securities Litigation Reform Act of 1995. All statements other than statements of historical fact are "forward-looking statements" for purposes of this Annual Report on Form 10-K for the fiscal year ended December 31, 2021, or Annual Report on Form 10-K. In some cases, you can identify forward-looking statements by terminology such as "anticipate," "believe," "continue," "could," "estimate," "expects," "intend," "may," "plan," "potential," "predict," "project," "should," "will," "would" or the negative or plural of those terms, and similar expressions. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements are subject to certain risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other "forward-looking" information. Forward-looking statements include, but are not limited to, statements about:

- the severity and duration of the impact of the COVID-19 pandemic on our business, development programs and access to capital;
- our plans to develop and commercialize our product candidates;
- the timing of execution of planned clinical trials and the availability of data from our clinical trials;
- our expectation that the efficacy and safety data from our Phase 3 registration trials, if positive, will be sufficient to support submission of a new drug application, or NDA, to the U.S. Food and Drug Administration, or FDA;
- our ability to obtain grants or other government funding to develop our product candidates;
- our ability to take advantage of benefits offered by current and pending legislation related to the development of products addressing antimicrobial resistance;
- the timing of and our ability to file, obtain and maintain regulatory filings for our product candidates;
- the clinical utility of our product candidates and their potential advantages compared to other treatments;
- our commercialization, marketing and distribution capabilities and strategy;
- our ability to establish and maintain arrangements for the manufacture of our product candidates;
- our ability to establish and maintain collaborations and to recognize the potential benefits of such collaborations;
- our estimates regarding the market opportunities for our product candidates;
- our intellectual property position and the duration of our patent rights;
- our estimates regarding anticipated operating losses, needs for additional funds and capital requirements and our ability to obtain such financing;
- political, social and economic instability, natural disasters or public health epidemics in countries where we or our collaborators do business;
- the substantial influence and control that Innoviva, Inc. and its affiliates, or Innoviva, may exert on actions requiring stockholder vote; and
- our estimated needs for and ability to raise additional financing, and our ability to continue as a going concern.

Factors that may cause actual results to differ materially from current expectations include, among other things, those set forth in Part I, Item 1A, "Risk Factors," herein and for the reasons described elsewhere in this Annual Report

on Form 10-K. These statements involve substantial known and unknown risks, uncertainties and other factors that may cause our actual results, level of activity, performance or achievements to differ materially from those currently anticipated. Forward-looking statements are neither historical facts nor assurances of future performance.

This Annual Report also contains estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources that we cannot independently verify, but believe to be reliable.

In this Annual Report on Form 10-K, unless otherwise stated or as the context otherwise requires, references to “Entasis,” “the Company,” “we,” “us,” “our” and similar references refer to Entasis Therapeutics Holdings Inc. and its wholly owned subsidiaries. The trademarks, trade names and service marks appearing in this Annual Report on Form 10-K are the property of their respective owners.

PART I

Item 1. BUSINESS

Overview

We are an advanced, late clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of targeted antibacterial products that address high unmet medical needs to treat serious infections caused by multidrug-resistant pathogens. On February 1, 2022. our Board of Directors received a preliminary, non-binding proposal from our majority stockholder, Innoviva Inc., or Innoviva, to acquire all the outstanding equity securities of the Company that are not currently owned by Innoviva for a per share consideration of $1.80, payable in cash. The offer letter delivered by Innoviva to our Board of Directors is publicly available in the Schedule 13D amendment dated February 1, 2022, filed by Innoviva with the Securities and Exchange Commission, or SEC. Our Board of Directors, which does not include any members appointed by or affiliated with Innoviva, has retained MTS Health Partners, L.P. and Covington & Burling, LLP to explore alternatives and to assist the Board of Directors in its evaluation of the proposal consistent with its fiduciary duties.

Our lead product candidate, sulbactam-durlobactam, or SUL-DUR, is an intravenous, or IV, combination of sulbactam, an IV β-lactam antibiotic, and durlobactam, a novel broad-spectrum IV β-lactamase inhibitor, or BLI, that we are developing for the treatment of pneumonia and bloodstream infections caused by carbapenem-resistant *Acinetobacter baumannii*, or *Acinetobacter*. Based on current carbapenem resistance rates, we estimate there are in excess of 250,000 hospital-treated carbapenem-resistant *Acinetobacter* infections annually across the United States, Europe, the Middle East and China for which significant morbidity and mortality exists due to limited treatment options. We initiated ATTACK (***A****cinetobacter* **T**reatment **T**rial **A**gainst **C**olistin), our single Phase 3 registration trial in 2019, and announced positive top-line Phase 3 data in October 2021 demonstrating that the primary efficacy and safety objectives had been achieved. Specifically, the results indicated non-inferiority in 28-day all-cause mortality in patients with carbapenem-resistant *Acinetobacter* infections and a statistically significant higher clinical cure rate compared to colistin. SUL-DUR also had a favorable safety profile when compared to colistin with a statistically significant reduction in nephrotoxicity. Based on the success of ATTACK and the totality of the SUL-DUR preclinical and clinical data, we also announced our intention to file a new drug application, or NDA, with the United States Food and Drug Administration, or FDA, in mid-2022. SUL-DUR has been awarded Fast Track status designation providing potential eligibility for accelerated approval and priority review, if relevant criteria are met, following acceptance of our submission by the FDA. With the support of our partner Zai Lab (Shanghai) Co., Ltd., or Zai Lab (Nasdaq: ZLAB), we enrolled approximately 25% of the ATTACK trial in China and combined with the strength of the overall SUL-DUR data set, we believe the data will also support a regulatory submission in China. Zai Lab has an exclusive license to develop and commercialize SUL-DUR in mainland China as well as the broader Asia-Pacific region.

Our second late-stage product candidate, zoliflodacin, is a novel orally administered molecule being developed for the treatment of uncomplicated gonorrhea. The bacterial pathogen responsible for gonorrhea is *Neisseria gonorrhoeae*, or *N. gonorrhoeae*. Intramuscular injections of ceftriaxone now represent the only U.S. Centers for Disease Control and Prevention, or CDC, recommended treatment option for the estimated 1.6 million annual cases of gonorrhea in the United States. We believe there is a growing unmet need for a single-dose oral antibiotic that will reliably treat patients with gonorrhea, including infections caused by multidrug-resistant strains of *N. gonorrhoeae*, which are emerging globally. The Phase 3 registration trial, initiated in September 2019, is sponsored by our nonprofit collaborator, the Global Antibiotic Research and Development Partnership, or GARDP, which as the sponsor is also responsible for all Phase 3 clinical trial and pharmaceutical development expenses. GARDP has commercial rights to zoliflodacin in up to 168 low- and select middle-income countries, while Entasis retains commercial rights in the major markets in North America, Europe and Asia-Pacific. Based on current enrollment rates, we anticipate the trial to be fully enrolled in 2023.

Our third product candidate is ETX0282CPDP which is a combination of a novel, oral BLI, ETX0282, with cefpodoxime proxetil or CPDP, which has the potential to address complicated urinary tract infections, or cUTIs, including those caused by multidrug-resistant *Enterobacteriaceae*. We believe there is a significant unmet need for new oral antibiotics to reliably treat the estimated 3 to 4 million patients diagnosed annually with cUTIs. We have reported preliminary Phase 1 trial results, and we are now seeking a partner to help further advance ETX0282CPDP through additional clinical trials. This program was previously supported by the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator program, or CARB-X.

We are also advancing the development of a novel class of antibiotics, non β-lactam inhibitors of penicillin-binding proteins, or NBPs. We believe NBPs constitute a potential new class of Gram-negative antibacterial agents that are designed to target a broad spectrum of multidrug resistant bacterial pathogens that overcome the main source of β-lactam resistance which is driven by β-lactamase activity. This novel class of agents is designed to potentially target a broad spectrum of multidrug resistant bacterial pathogens that are part of the CDC/World Health Organization, or WHO, list of high unmet medical need or ESKAPE pathogens. We selected ETX0462 as the initial clinical candidate for this program and with support from CARB-X we are currently working to complete additional pre-clinical activities to enable the program to advance into a Phase 1 clinical trial. In June 2020, we were awarded a contract from the National Institutes of Health, or NIH, to support research towards developing additional NBP molecules with expanded Gram-negative spectrum from this novel class. This research program, designated NBP2, is attempting to target *Klebsiella*, *Pseudomonas* and *E. coli* from the ESKAPE list of pathogens. In July 2021, we successfully completed the first milestones for the program and were awarded the Option 1 Period of the program to proceed with further optimization, beginning August 1, 2021. Subject to achieving pre-defined milestones, the contract is expected to sufficiently fund activities to achieve submission of an investigational new drug, or IND, application to the FDA.

Our Strategy

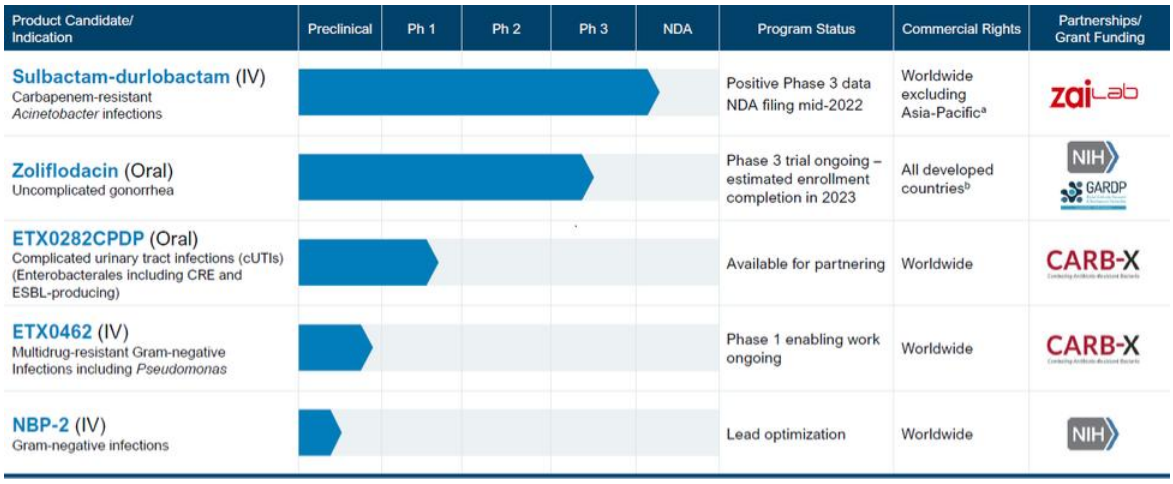
Our goal is to maximize the value of our targeted antibacterial agents for the treatment of serious infections caused by multidrug-resistant pathogens. Our strategy includes the following key components:

- **Advance our lead product candidate SUL-DUR through NDA filing and FDA approval.** Our lead product candidate, SUL-DUR, is a novel IV antibiotic that is a combination of sulbactam, an IV β-lactam antibiotic, and durlobactam, our novel BLI, that we are developing for the treatment of a variety of serious infections caused by carbapenem-resistant *Acinetobacter*. We announced positive Phase 3 top-line data in October 2021, and based on the totality of our preclinical and clinical data, we announced our intention to file an NDA in mid-2022. SUL-DUR has been awarded Fast Track status designation providing potential eligibility for accelerated approval and priority review, if relevant criteria are met, following acceptance of our submission by the FDA. We believe SUL-DUR has the ability to improve outcomes of patients with multidrug-resistant *Acinetobacter* infections, reducing their overall mortality.

- **Advance our existing pipeline of pathogen targeted antibiotics for infections poorly treated by existing generic or branded antibiotics.** In addition to SUL-DUR, we believe that our pipeline product candidates present differentiated and compelling solutions for infections caused by certain multidrug resistant pathogens. Zoliflodacin is an oral, potential single-dose treatment for uncomplicated gonorrhea caused by *N. gonorrhoeae*, including multidrug-resistant strains. ETX0282CPDP is a potential treatment of cUTIs, including those caused by multidrug-resistant *Enterobacteriaceae*. ETX0462 is being developed to address multidrug-resistant *Pseudomonas* and biothreat pathogens. To support the development of our pipeline we have successfully collaborated with commercial as well as nonprofit organizations, government agencies and other third parties, including Zai Lab, GARDP, the National Institute of Allergy and Infectious Disease, or NIAID, the U.S. Department of Defense, or DOD, and CARB-X, and the Repair Fund, to secure financial and technical support of our research and development efforts.

Product Portfolio

The following table summarizes the status of our product candidates and preclinical programs:



a. Zai Lab has licensed exclusive rights to SUL-DUR in the Asia-Pacific region.

b. GARDP will fully fund the Phase 3 clinical trial and pharmaceutical development activities and has commercial rights in WHO defined low-income and specified middle-income countries. We have retained commercial rights in all major markets in North America, Europe and Asia-Pacific.

Antibiotics Background

The introduction of antibiotics for the treatment of bacterial infections is recognized as one of the most transformative events in medicine. Antibiotics either kill bacteria (cytocidal) or inhibit bacterial cell growth (cytostatic), in both cases allowing the body's natural immune system to clear the bacteria. After penicillin, a β-lactam class antibiotic, entered the market in the early 1940s, antibiotics became one of the most commonly prescribed drugs in history. The modern era of antibiotics began in the 1950s with the discovery and commercialization of a number of antibiotic classes and molecules including additional β-lactams, tetracyclines, fluoroquinolones, aminoglycosides and polymyxins.

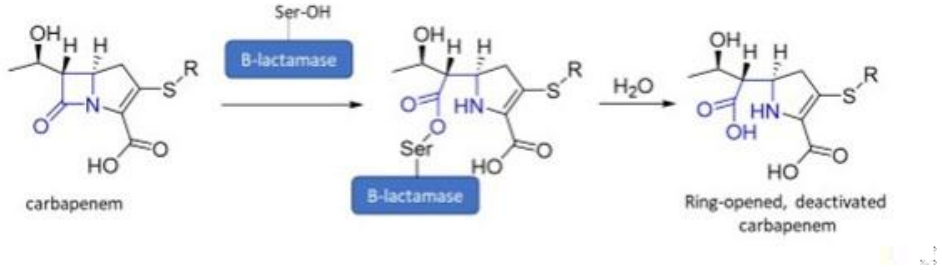
There are two main varieties of bacteria, Gram-positive and Gram-negative, which are identified using a common laboratory staining test known as the "Gram stain." Gram-positive bacteria are surrounded by a single membrane, while Gram-negative bacteria have both an inner membrane and an outer membrane. Due to this increased complexity, it has historically been more challenging to develop products that target Gram-negative bacteria, such as *Pseudomonas*, *Acinetobacter* and *Enterobacteriaceae*, a family of related organisms that includes the Enterobacter species, *E. coli*, and *Klebsiella pneumonia*. In the United States, approximately 8.2 million bacterial infections are treated in the hospital annually. Approximately 60% of hospital-treated infections are Gram-negative, and over 140,000 patients treated in the hospital for Gram-negative infections die annually in the United States.

One of the most widely used antibiotic classes are β-lactams due to the combination of their attractive safety and efficacy profile. β-lactams work by inhibiting penicillin binding proteins, or PBPs, proteins that play an important role in bacterial cell wall synthesis and are essential for the growth and reproduction of bacteria. β-Lactam antibiotics consist of all antibiotic agents that contain a β-lactam ring in their molecular structures. Among β-lactam antibiotics, penicillin derivatives and cephalosporins are the most commonly used. Carbapenems, another class of β-lactam antibiotics, are generally more effective against Gram-negative multidrug resistant pathogens; but to preserve their activity, they are often limited for use as a last resort.

Antibiotic Resistance

Antibiotic resistance is a direct consequence of antibiotic use. No sooner was penicillin adopted in clinical use, that the first cases of penicillin-resistant infections were reported. Indeed, resistance to penicillin, as was subsequently found to be the case for other natural product-derived antibiotics, pre-dates its medicinal use. This issue has escalated in the modern era, as millions of metric tons of antibiotics have been produced for human therapeutic use and use in agriculture and animal husbandry. This increased demand and use of antibiotics has contributed significantly to the emergence of resistant strains. For a period, the discovery of new antibiotics kept pace with the emergence of resistance; however, this is no longer the case and as a result, clinicians now commonly resort to using a combination of suboptimal antibiotics in an attempt to treat antibiotic resistant infections. For example, in the United States and European Union from 2004 to 2015, the use of last-resort antibiotics, carbapenems and polymyxins, increased annually by 6% and 8%, respectively. The negative consequences of this approach are twofold, as inappropriate antibiotic therapy leads to poorer outcomes for patients and potential subinhibitory and subtherapeutic antibiotic concentrations can further promote the development of antibiotic resistance.

Antibiotic resistance is now a global health threat and when bacteria develop resistance to drugs in at least three or more antibiotic classes, they are commonly referred to as multidrug-resistant. Bacteria use a number of mechanisms to develop resistance to antibiotics. Resistance to β-lactam antibiotics primarily occurs when bacteria acquire foreign genes that encode β-lactamases, enzymes that inactivate the β-lactam antibiotic by breaking apart the β-lactam ring, which renders the antibiotic inactive. Below, a β-lactamase enzyme (blue box) is shown binding to and cleaving the blue β-lactam ring of a carbapenem antibiotic. β-lactamases are widely prevalent and are classified into four classes, Classes A, B, C and D. Since 1976, researchers have discovered and developed β-lactamase inhibitors (BLIs) that essentially restore the efficacy of the β-lactam antibiotic by neutralizing β-lactamase enzymes. Despite the discovery and regulatory approval of novel BLIs, currently marketed BLIs do not broadly inhibit Class D β-lactamases, which are a particular concern in infections caused by multidrug-resistant *Acinetobacter*.



Antibiotic-resistant infections often result in high morbidity and, in many cases, mortality. According to the article "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis" published in The Lancet on February 12, 2022, antimicrobial resistance was associated with approximately 4.95 million deaths and directly attributed to 1.27 million deaths in 2019. In the United States alone, antibiotic-resistant infections are estimated to add $20 billion per year to healthcare costs. Due to the limitations of current treatment options and growing antibiotic resistance rates, the pathogens targeted by our current product candidates, *Acinetobacter, Pseudomonas,* CRE and *N. gonorrhoeae*, are all identified as high priority targets by the CDC and WHO, and the Infectious Diseases Society of America, or IDSA.

Rising antibiotic resistance has catalyzed a global call to action. Funding from government and nonprofit agencies for antibiotic research and development and an improved regulatory environment support the efficient development of novel antibiotics targeted at unmet need areas. GARDP, NIAID, the Biomedical Advanced Research and Development Authority, or BARDA, the Defense Advanced Research Projects Agency, or DARPA, the DOD, and the Innovative Medicines Initiative, all offer funding or services to support research and development of novel antibiotics.

Changes in the legal/policy landscape in the United States have also highlighted the growing importance of addressing antimicrobial resistance. Proposed legislation includes the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms Act, or DISARM, which calls for payment of qualified infectious disease products, or QIDPs, outside of the hospital diagnosis-related group, or DRG, resulting in potentially higher Medicare reimbursement for those novel antibiotics designated as QIDPs. Qualifying hospitals would be required to participate in a specified antibiotic stewardship program in order to be eligible for higher payment. More recently, this legislation was reintroduced in the U.S. House of Representatives in June 2021, which aims to amend title XVIII of the Social Security Act to encourage the development and use of DISARM antimicrobial drugs, and for other purposes. The Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2020, or PASTEUR Act, was introduced to provide a mechanism for funding designated “critical need antimicrobial” drugs following FDA approval. In return, patients covered by federal insurance programs will receive these drugs at no cost. These contracts could range from $750 million to $3 billion in value. In October 2021, the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, or PACCARB, authored a letter to the Honorable Xavier Becerra Secretary, Department of Health and Human Services recommending the passage of both DISARM and PASTEUR and the antimicrobial stewardship provisions contained within each act.

Our Product Candidates

Sulbactam-durlobactam (SUL-DUR)

Overview

Our lead product candidate, SUL-DUR, is a novel IV antibiotic with broad spectrum β-lactamase coverage including Classes A, C and D. The product is a combination of sulbactam, a β-lactam antibiotic, and durlobactam, our novel BLI, that we are developing for the treatment of a variety of serious infections caused by carbapenem-resistant *Acinetobacter*. We have completed three separate Phase 1 clinical trials, including one evaluating the penetration of SUL-DUR into the lung and one in renally impaired patients. Subsequently, we completed a Phase 2 clinical trial in patients with cUTIs. We initiated ATTACK, our single Phase 3 registration trial in 2019, that evaluated SUL-DUR in patients with confirmed carbapenem-resistant *Acinetobacter* pneumonia and/or bloodstream infections. We announced positive top-line Phase 3 data in October 2021 and based on our positive top-line Phase 3 data and the totality of our preclinical and clinical data, announced our intention to file an NDA with the FDA in mid-2022. We believe SUL-DUR has the ability to improve outcomes of patients with multidrug-resistant *Acinetobacter* infections, reducing their overall mortality.

Acinetobacter

Acinetobacter is a Gram-negative, opportunistic human pathogen that predominantly infects critically ill patients often resulting in severe pneumonia and bloodstream infections but can also infect other body sites as well. Once thought to be mostly benign, *Acinetobacter* is now considered a global threat in the healthcare setting due in part to its ability to acquire multidrug resistance at rates not previously seen in other bacteria. In addition, *Acinetobacter* has the ability to remain viable for up to 100 days in dry conditions and easily spreads via air or water droplets, which explains why the pathogen can often be found in many locations in the intensive care unit, or ICU, including bedrails, bedside tables, monitors of mechanical ventilators, intravenous pumps, door handles, stethoscopes and many other locations. Of significant concern, one study reported greater than 98% of *Acinetobacter* isolates in an ICU from non-clinical sources such as bedrails and door handles, were determined to be multidrug resistant.

Pneumonia and bloodstream infections caused by drug-resistant *Acinetobacter* can have mortality rates approaching 50%. Antibiotic-resistance rates of *Acinetobacter* to current standard-of-care treatments are some of the highest reported, between 30% and 50% in the United States and greater than 90% in parts of Europe and Asia. *Acinetobacter* resistance to β-lactams is primarily driven by the expression of Class D β-lactamases, often in combination with Class A and/or Class C β-lactamases. There are currently no effective antibiotics indicated for the treatment of multidrug-resistant *Acinetobacter* infections. Durlobactam is the first clinical-stage BLI with sufficient broad-spectrum activity against class A, C, and D β-lactamases to potentially restore the efficacy of β-lactam antibiotics against multidrug-resistant *Acinetobacter*.

Sulbactam, the β-lactam antibiotic used in SUL-DUR has superior microbiological potency against *Acinetobacter* compared to other β-lactam antibiotics based on *in vitro* and *in vivo* analyses. Historically, physicians used sulbactam to successfully treat *Acinetobacter* infections before development of broad β-lactamase mediated resistance rendered sulbactam on its own largely ineffective. We believe our data demonstrates that combining durlobactam with sulbactam can effectively restore the activity of sulbactam against multidrug-resistant strains of *Acinetobacter*.

Market Opportunity

We estimate that there are 180,000 to 220,000 hospital-treated *Acinetobacter* infections annually in the United States and Europe, of which 65,000 to 100,000 are carbapenem-resistant *Acinetobacter* infections, which we regard as our initial target markets for SUL-DUR. We also believe there could be a significant market opportunity in Asia-Pacific, Central and South America, Russia and the Middle East given resistance rates exceeding 80% in some countries. If approved, we believe SUL-DUR has the potential to address the issues of resistance facing existing regimens, which is currently limiting the utility of the carbapenems, and tolerability, which is a concern with regimens containing colistin. There are currently no antibiotics indicated for the treatment of carbapenem-resistant *Acinetobacter* infections.

Clinical Development Plan

Completed Clinical Trials

Phase 3 registration trial: We completed ATTACK, a Phase 3 registration trial of SUL-DUR for the treatment of patients with carbapenem-resistant *Acinetobacter* infections, with positive top-line data announced in October 2021. ATTACK enrolled 207 patients at 95 clinical sites in 16 countries. This was a two-part trial with Part A being the randomized, comparative portion (SUL-DUR vs colistin) in patients with documented *Acinetobacter* hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VAPB), ventilated pneumonia (VP), or bacteremia, and Part B being an open-labeled portion including *Acinetobacter* infections resistant to, or having previously failed colistin or polymyxin B treatment. Baseline *Acinetobacter* isolates tested were greater than 95% carbapenem resistant.

SUL-DUR met the primary efficacy endpoint of 28-day all-cause mortality compared to colistin in the CRABC m-MITT population of Part A. SUL-DUR mortality was 19.0% (12/63) compared to 32.3% (20/62) in the colistin arm (treatment difference of -13.2%; 95% CI: -30.0, 3.5). Similar trends were demonstrated in 28-day and 14-day all-cause mortality favoring SUL-DUR across all study populations evaluated to date. A statistically significant difference in clinical cure at Test of Cure (TOC) was observed with 61.9% in SUL-DUR arm compared to 40.3% in the colistin arm (95% CI 2.9-40.3). In Part B, the 28-day all-cause mortality was 17.9% (5/28) and consistent with that observed in Part A.

Safety analyses from a total of 177 patients suggested that SUL-DUR was generally well-tolerated with a favorable safety profile compared to colistin. SUL-DUR met the primary safety objective with a statistically significant reduction in nephrotoxicity as measured by the RIFLE classification for acute kidney injury. SUL-DUR nephrotoxicity was 13.2% (12/91) versus 37.6% (32/85) in the colistin arm (p = 0. 0002). Overall adverse events (AEs) in the safety population were comparable between treatment groups with 87.9% (80/91) in the SUL-DUR arm vs. 94.2% (81/86) in the colistin arm in Part A, 89.3% (25/28) in Part B. Drug related AEs were 12.1% (10.7% in Part B) with SUL-DUR compared to 30.2% with colistin. The most common non-infectious AEs (≥10%) in the SUL-DUR arm were diarrhea (16.5%), allergic and hypersensitivity reactions (16.5%), anemia (13.2%) and hypokalemia (12.1%) in Part A. These AEs were also >10% in the colistin arm as was acute kidney injury.

We believe that the data from the ATTACK trial, data from our other clinical trials of SUL-DUR and non-clinical data will be sufficient to submit an NDA to the FDA in mid-2022.

Phase 2 clinical trial in cUTI patients: We completed a Phase 2 clinical trial in cUTI patients to provide additional safety and pharmacokinetic, or PK, data as well as efficacy data against carbapenem-resistant pathogens. Eighty patients were randomized to receive either a dose of SUL-DUR or placebo every six hours for seven days. Patients in both arms also received background therapy, which is current standard-of-care, with 500 mg of imipenem, or IMI, administered through IV every six hours. There were no serious adverse events reported and the adverse event profile of SUL-DUR plus IMI was similar to that of the IMI comparator arm. PK data observed in the Phase 2 trial was consistent with the PK data observed in the Phase 1 clinical trial in healthy volunteers.

We have completed three Phase 1 clinical trials, highlighted below, in addition to a Phase 2 clinical trial in patients with cUTIs. In all of these clinical trials, SUL-DUR was observed to be generally well tolerated.

Four-part Phase 1 first-in-human trial: Our four-part Phase 1 first-in-human clinical trial was conducted in Australia in 124 healthy volunteers. SUL-DUR was generally well tolerated, with no dose-related systemic adverse events or drug-related serious adverse events reported. SUL-DUR also exhibited linear dose-dependent increases in exposure and PK parameters across the dose range studied.

Phase 1 lung trial: Our Phase 1 lung trial assessed the concentration of SUL-DUR in lung fluid, an important metric to understand, because ATTACK includes patients with pneumonia and lack of appropriate lung tissue penetration has been found to contribute to reduced efficacy. We believe that the levels of SUL-DUR in the lung fluid achieved in this trial support its continued development as a potential treatment for pneumonia caused by *Acinetobacter*.

Phase 1 renal trial: Our Phase 1 renal trial analyzed serum levels in renally impaired patients and provided data to enable the development of a dose adjustment protocol for the type of patient targeted in our ongoing Phase 3 registration trial.

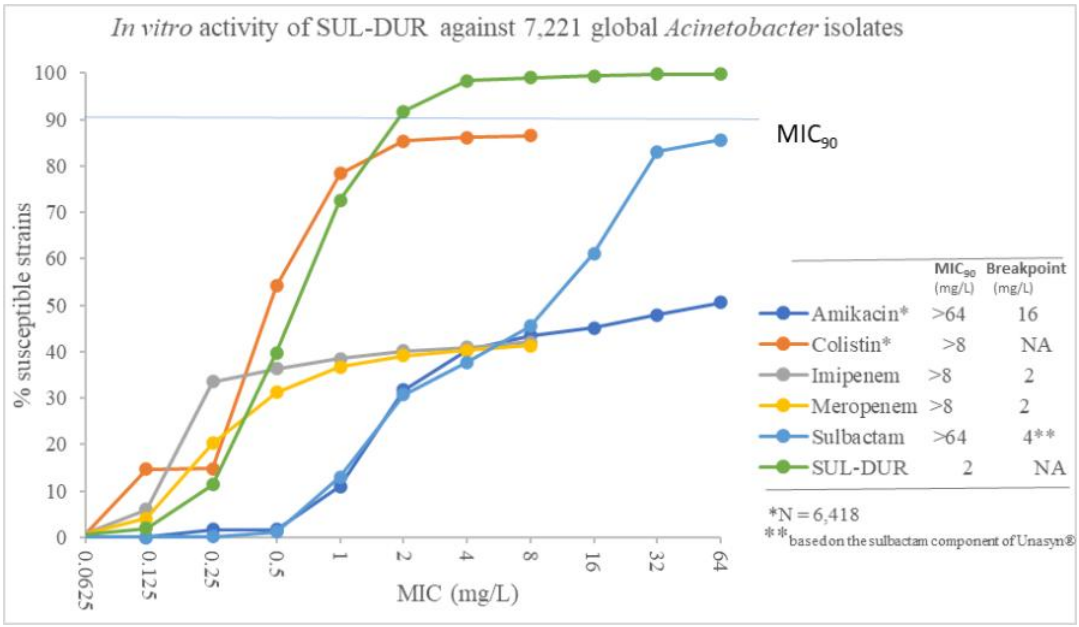
We submitted an IND for SUL-DUR to the FDA in June 2017, and the FDA notified us in July 2017 that we could proceed with this program. The FDA granted Fast Track and QIDP designation for SUL-DUR in September 2017 for the treatment of hospital-acquired and ventilator-acquired bacterial pneumonia and bloodstream infections due to *Acinetobacter*.

Global Acinetobacter Surveillance Data

We designed durlobactam to achieve broad activity against a wide range of β-lactamases, including Classes A, C and D, unlike currently marketed BLIs that primarily cover only Class A and Class C β-lactamases. Durlobactam is the first BLI in clinical development with such a broad spectrum of *in vitro* activity.

SUL-DUR has also exhibited potent microbiological activity against *Acinetobacter* strains *in vitro.* Over a series of studies summarized in the figure below, we have compared the effectiveness of SUL-DUR, sulbactam alone and comparators in inhibiting 7,221 strains of *Acinetobacter* that were collected from patients around the world between 2011 and 2020. Amikacin and colistin were tested against 6,418 of the 7,221 strains. The plot in the figure below

presents the cumulative percentage of these strains inhibited by increasing concentrations of each of the tested compounds. Sulbactam alone, as well as most of the other marketed antibiotics, had a very high MIC_{90} value of 64 mg/L, meaning that concentrations of 64 mg/L or greater were required to inhibit growth of 90% of the strains. The corresponding breakpoints, which are established by the Clinical & Lab Standards Institute, or CLSI, as the specified concentrations for each antibiotic that define whether a strain is considered resistant, are significantly lower than their MIC_{90} values. If the MIC_{90} of a drug is lower than its CLSI breakpoint, then that drug would be expected to be effective against more than 90% of the strains. If a drug's MIC_{90} is higher than its breakpoint, the drug would not be expected to have broad efficacy against those strains. This cumulative analysis suggests that recent global strains of *Acinetobacter* are resistant to all the comparator antibiotics other than colistin, consistent with their significantly diminished clinical utility against *Acinetobacter* infections. In contrast, SUL-DUR had very potent activity, with a much lower MIC_{90} of 2 mg/L. This is lower than the CLSI breakpoint for sulbactam, which is 4 mg/L (in Unasyn®, a combination of sulbactam and ampicillin), suggesting that our chosen target exposure levels of SUL-DUR may be effective against more than 90% of global, multidrug resistant *Acinetobacter* strains. A subset of 926 isolates out of the 7,221 strains tested were from Chinese hospitals collected in 2016-2018. 831 of the 926 (84.6%) Chinese isolates were carbapenem-resistant. In contrast, SUL-DUR showed potent activity against this subset, with an MIC_{90} of 2 mg/L and 97.9% of isolates susceptible to ≤ 4 mg/L of SUL-DUR.



Competition

We are initially developing SUL-DUR for the treatment of multidrug-resistant *Acinetobacter* infections. Due to rising resistance rates, standard-of-care treatment for multidrug-resistant *Acinetobacter* infections often includes a combination of several last-line treatment options, including carbapenems, tetracyclines, polymyxins, and other generically available agents. Despite using best available therapy, mortality rates of patients with multidrug-resistant *Acinetobacter* infections is reported as high as 50%. As of the date of this report, we are not aware of any marketed antibiotic that is indicated for the treatment of multidrug-resistant *Acinetobacter* infections; however, we are aware of other potentially competitive products that have shown *in vitro* activity against some strains of *Acinetobacter.* Melinta Therapeutics Inc. currently markets minocycline while La Jolla Pharmaceutical Company, Inc. currently markets eravacycline for complicated intra-abdominal infections. Although recently approved for treating cUTIs, Fetroja®, from Shionogi & Co., Ltd., includes in its label a specific warning of an observed increase in all-cause mortality in patients with carbapenem-resistant Gram-negative bacterial infections that were treated with the drug. BioVersys AG reported in

March 2021 that their lead program BV100 is progressing in Phase 1 clinical development specifically for multidrug-resistant *Acinetobacter* infections.

Manufacturing Approach

We contract with third party contract manufacturing organizations for the manufacture, packaging and labeling of sulbactam and durlobactam for preclinical studies and clinical trials, and we intend to continue to use third party manufacturing organizations in connection with any future commercialization of SUL-DUR. We continue to work with our current manufacturing partners to improve processes to increase our manufacturing capacity, reduce overall cost of manufacturing, and implement other steps toward commercial readiness. Our current manufacturing partners produce drug substance and drug product pursuant to agreements that require compliance with current Good Manufacturing Practices (cGMP). We are currently negotiating commercial supply agreements with third party manufacturing organizations and will look to finalize these agreements as part of commercial readiness.

Commercial Approach

In the United States, our commercial strategy is driven by our understanding of where *Acinetobacter* infections are known to exist. Given that *Acinetobacter* infections more commonly occur in immunocompromised patients, treatment settings for these patients are frequently large intensive care units (ICUs), specialized centers like transplant, cancer, and burn, outpatient long-term acute centers (LTACs) and home infusion.

SUL-DUR has been developed specifically for multi-drug resistant *Acinetobacter* infections and we believe the unmet need and value proposition of SUL-DUR will support its use for treating infections caused by this serious Gram-negative pathogen. This value proposition includes:

1. *Acinetobacter* infections currently cost lives. There is an urgent, global unmet medical need due to the limitations of currently available treatment options. Published mortality rates of *Acinetobacter* infections treated with best available therapy are reported to exceed 50%.

2. *Acinetobacter* infections currently cost time. These serious infections directly lead to time in a hospital where hospital length of stay is often measured in months or weeks instead of days.

3. *Acinetobacter* infections currently cost money. Given the limitations described above, carbapenem-resistant *Acinetobacter* infections are reported to be one of the costliest to treat, exceeding $75,000 per case based upon published literature.

4. We believe the data from ATTACK, combined with our overall preclinical and clinical data package, clearly demonstrate an efficacy and safety benefit of SUL-DUR over colistin in treating carbapenem resistant *Acinetobacter* infections.

Current *Acinetobacter* treatment protocols allow for clear positioning of SUL-DUR. Patients with suspected *Acinetobacter* infections are frequently treated with a broad-spectrum antibiotic, commonly a carbapenem, as first-line therapy. If susceptibility testing identifies that the causative bacterial pathogen is carbapenem-resistant *Acinetobacter*, the patient is then frequently switched to a colistin-based antibiotic regimen in an attempt to successfully treat the infection. Published literature, however, reports greater than 50% mortality rates using colistin-based regimens. We believe that the data from the ATTACK Phase 3 registration trial demonstrate improved efficacy and safety profiles, that could result in SUL-DUR, if approved, being preferred to a colistin-based regimen for the treatment of multidrug-resistant, including carbapenem-resistant, *Acinetobacter* infections.

Multidrug-resistant *Acinetobacter* infections also present a significant unmet medical need in China and across the broader Asia/Pacific territory. Our collaboration and license agreement with Zai Lab, which included their participation in the ATTACK Phase 3 registration clinical trial, provides a potentially accelerated path for regulatory approval and commercialization in China and Asia-Pacific territories. Zai Lab supported the enrollment of approximately 25% of the evaluable patients in ATTACK from China, which we believe will support a regulatory

submission in China. Under our agreement with Zai Lab, we receive upfront, milestone and royalty payments in addition to payment of certain Phase 3 registration clinical trial costs. We maintain 100% of the rights and associated economics in North America and Europe. Outside of the United States, we intend to work with multi-national pharmaceutical companies to leverage their commercialization capabilities in territories not covered by our agreement with Zai Lab.

Zoliflodacin

Overview

Our second late-stage product candidate is zoliflodacin, a potential single oral dose cure for the treatment of uncomplicated gonorrhea caused by the bacterial pathogen *N. gonorrhoeae*. Gonorrhea is an area of significant medical need and zoliflodacin is the only novel single dose treatment in development that provides a potential monotherapy oral alternative to intramuscular injections of ceftriaxone for the treatment of gonorrhea, including infections caused by drug-resistant strains. Zoliflodacin targets the validated mechanism of action of the fluoroquinolone class of antibiotics but does so in a novel manner to avoid existing fluoroquinolone resistance. We have completed several Phase 1 clinical trials and a Phase 2 clinical trial of zoliflodacin in patients with uncomplicated gonorrhea. In collaboration with GARDP, in 2019 we initiated a single Phase 3 registration trial of zoliflodacin in patients with uncomplicated gonorrhea. GARDP will fund all the Phase 3 clinical trial and pharmaceutical development costs and in return will receive commercial rights for zoliflodacin in WHO-defined low-income and select middle-income countries. We have retained commercial rights in all other countries, including the major markets in North America, Europe and Asia-Pacific.

Gonorrhea

Uncomplicated gonorrhea is an *N. gonorrhoeae* infection of the urethra, cervix, pharynx or rectum, and is more common than complicated gonorrhea, which includes spread of the infection to other tissues and potentially the bloodstream. Gonorrhea can be associated with serious complications, including pelvic inflammatory disease, ectopic pregnancy and infertility, as well as an increased risk of human immunodeficiency virus, or HIV. Despite the continued use of effective antibiotics, it remains one of the most common sexually transmitted bacterial infections in the world with an estimated 87 million people worldwide infected each year. The occasional absence of symptoms, more frequent in women, is thought to be one reason for sustained levels of infection. Reports on the lack of a robust immune response to infection by *N. gonorrhoeae* in humans is also thought to facilitate not only initial infection but also reinfection. Efforts to develop a prophylactic vaccine for *N. gonorrhoeae* continue; however, to date all have failed, again thought to be the result of insufficient or absent protective immunity to *N. gonorrhoeae* infections in humans. Taken together, antibiotics remain the mainstay for treating uncomplicated gonorrhea caused by *N. gonorrhoeae.*

N. gonorrhoeae is the bacterial pathogen responsible for gonorrhea and has a strong propensity for uptake of chromosomal DNA from other genera of *Neisseria* which allows the bacteria to accumulate many mutations in chromosomal genes leading to frequent resistance of antibiotics. For example, penicillin was introduced for *N. gonorrhoeae* infections in 1943, and initial resistance was reported in 1945. Fluoroquinolone antibiotics were first used to treat gonorrhea in 1949 and have been one of the most successful classes of antibiotics against *N. gonorrhoeae*, but even so resistance was identified in 1969. One member of this class, ciprofloxacin, was introduced in 1980 and resistance was identified in 1990. More recently cephalosporin antibiotics, notably cefixime, had been widely used for the treatment of gonorrhea due to their oral administration along with a favorable efficacy and safety profile, although resistance by *N. gonorrhoeae* has been reported since 2007. As widespread use of these antibiotics drove the emergence of drug-resistant *N. gonorrhoeae* strains, treatment guidelines have subsequently been amended. Ceftriaxone is currently the only CDC-recommended option for the treatment of gonorrhea and, until recently, was administered with azithromycin, a broad-spectrum antibiotic, to provide coverage against other sexually transmitted diseases that tend to occur concurrently with gonorrhea. However, rising resistance of *N. gonorrhoeae* to azithromycin recently prompted the CDC to now recommend ceftriaxone monotherapy. Ceftriaxone is administered by intramuscular injection, which can be painful and may require patient monitoring by a healthcare administrator. Although ceftriaxone remains effective in most of the U.S., in Hawaii as well as in several countries, including China, Japan, Vietnam, South Korea, France and Spain, *N. gonorrhoeae* strains with resistance to azithromycin and ceftriaxone have been reported, prompting concerns that multidrug-resistant gonorrhea may become a major community health issue.

Market Opportunity

N. gonorrhoeae is an immediate global public health threat with 84.2 million cases worldwide in 2020 (WHO estimate). Cases of gonorrhea in the United States have reached an estimated 1.6 million per year. The WHO worldwide estimated of approximately 82.4 million new cases includes infected adolescents and adults aged 15–49 years. The CDC estimates that the cases of gonorrhea in the United States have been increasing at least 10% per year since 2009. In April 2021, the CDC announced that sexually transmitted diseases in the U.S. reached all-time high for 6th consecutive year, with approximately 2.6 million cases of chlamydia, gonorrhea & syphilis reported in 2019.

The results of a 2017-2018 survey of countries reporting decreased susceptibility, DS, or resistance, R, of *N. gonorrhoeae* to current antibiotics is reflected in the table below.

Antibiotic	Countries with DS or R
Oral ciprofloxicin	70/70 (100%)
Oral azithromycin	51/61 (84%)
Oral cefixime	24/51 (47%)
ceftriaxone	21/68 (31%)

Historically, to reduce the risk of spreading drug-resistant *N. gonorrhoeae*, the CDC has changed treatment guidelines when resistance rates to recommended first-line treatments reach 5%. Since 2015, there has only been one recommended treatment on CDC guidelines for gonorrhea: 250mg intramuscular injection of ceftriaxone plus 1g of oral azithromycin. In 2020 the CDC once again updated its treatment guideline, now recommending a 500mg intramuscular injection of ceftriaxone for treatment of uncomplicated gonorrhea. This follows a 2019 update in the United Kingdom where recommended empirical treatment of gonorrhea is now 1g intramuscular ceftriaxone monotherapy.

Clinical Development Plan

Ongoing Registration Trial

Phase 3 registration trial: In 2019, we announced the initiation of a global, multi-center Phase 3 registration trial in collaboration with GARDP who is conducting and funding all Phase 3 clinical trial and pharmaceutical development costs. Up to 18 clinical trial sites are planned across the U.S., Thailand, South Africa, the Netherlands and Belgium. Our Phase 3 registration trial is a multi-center, open-label, noninferiority trial in approximately 1,000 enrolled patients with uncomplicated gonorrhea who will be randomized on a 2:1 basis to receive either a single 3.0g oral dose of zoliflodacin or a regimen of 500mg intramuscular ceftriaxone plus 1g oral azithromycin. The primary endpoint will be the proportion of patients with microbiological cure at urethral or cervical sites, approximately six days after treatment. The Data Safety Monitoring Board, or DSMB, in May 2021 recommended to continue the study without modification. Despite the ongoing challenges with the COVID-19 pandemic, we have observed an increase in the enrollment rate during the past two quarters and based on current enrollment rates we anticipate completion of trial enrollment in 2023. Based on our discussions with the FDA, we believe that the efficacy data from this single Phase 3 registration trial, if positive, along with the data from our other clinical trials of zoliflodacin, will be sufficient to support the submission of an NDA to the FDA.

Completed Clinical Trials

Phase 2 clinical proof-of-concept trial: We have completed a multi-center, randomized, open-label Phase 2 clinical trial comparing a single oral dose of 2.0g or 3.0g of zoliflodacin to 500mg intramuscular ceftriaxone for the treatment of uncomplicated gonorrhea. In this trial, 179 randomized patients received treatment and zoliflodacin was generally well tolerated, with efficacy outcomes comparable to ceftriaxone. Microbiological eradication and clinical cure in urogenital infections with a single dose of zoliflodacin, the primary endpoint of the trial, was comparable to ceftriaxone, with 100% cure rate in both the 3.0g zoliflodacin and ceftriaxone groups in the per-protocol population. The results of this clinical trial were published in *The New England Journal of Medicine* in 2018.

Phase 1 clinical trial: We evaluated zoliflodacin in two Phase 1 clinical trials studying 72 healthy volunteers in total. In one trial, we evaluated PKs and tolerability in 48 subjects and food effects in 18 subjects, and in the second trial, we evaluated absorption, distribution, metabolism and excretion in six subjects. Zoliflodacin was generally well tolerated in these trials at doses we would expect to be clinically active for treating uncomplicated gonorrhea. Administration of a high-fat meal was associated with an increase in zoliflodacin plasma concentration, suggesting that zoliflodacin could be administered with or without food.

Preclinical Data

We have generated biochemical, microbiological and *in vivo* data on zoliflodacin. The data suggest that zoliflodacin retains potent activity against contemporary clinical isolates in the U.S., Europe, China, Thailand and South Africa that are resistant to other antibiotic classes including fluroquinolones, which was expected given its novel mechanism of action. In addition, the data show significant resistance against two of the four standard antibiotics indicated for gonorrhea, ciprofloxacin, a fluoroquinolone, and azithromycin, a macrolide.

Competition

We are initially developing zoliflodacin as a single oral dose treatment for uncomplicated gonorrhea. Gonorrhea is commonly treated with combination therapy intramuscular ceftriaxone injection and oral azithromycin, both generically available agents. Additional generic cephalosporins and fluoroquinolones are also prescribed, but not recommended as primary treatment options given current resistance rates. Gepotidacin, currently under development for a variety of infections by GlaxoSmithKline plc, is the only potentially competitive product candidate in late-stage clinical development that we are aware of that is being developed for the treatment of uncomplicated urogenital gonorrhea. A Phase 3 clinical trial (EAGLE-1) was initiated by GlaxoSmithKline in October 2019. A prior Phase 2 clinical trial revealed the emergence of resistance to gepotidacin in 2 urogenital microbiological failures following administration of a single oral dose. In an attempt to overcome this resistance, gepotidacin will be given in two oral doses in the EAGLE-1 clinical trial; a 4-tablet 3000 milligram (mg) oral dose at the study site followed by another 4-tablet 3000mg oral dose as an outpatient.

Manufacturing Approach

GARDP has partnered with third party contract manufacturing organizations for the manufacture of drug substance and drug product for zoliflodacin. These partners are capable of producing commercial scale quantities of zoliflodacin drug substance and drug product under cGMP conditions. GARDP will develop direct long-term commercial supply agreements for sales in their respective territories. As we execute upon our commercialization strategy for zoliflodacin, we intend to work with the established zoliflodacin manufacturing partners for our commercial supply.

Commercial Approach

Antibiotics to treat uncomplicated gonorrhea will typically be available through primary care physicians, outpatient clinics and emergency rooms, and numerous community sites. In addition, placement on CDC guidelines has historically driven awareness and uptake in the U.S. We have partnered with GARDP who will lead the commercialization of zoliflodacin in certain WHO-defined low-income and specified middle-income countries.

Zoliflodacin is a potential single dose cure (sachet in water) that can facilitate “expedited partner therapy” at home, which may lower the chance for a repeat infection from a partner. Expedited partner therapy, or EPT, is the clinical practice of treating the sex partners of patients diagnosed with chlamydia or gonorrhea by providing prescriptions or medications to the patient to take to his/her partner without the health care provider first examining the partner. Within the United States, EPT is permissible in 45 states, potentially allowable in 4 states and is only prohibited in one state.

ETX0282CPDP

Overview

Our third product candidate is ETX0282CPDP for the potential oral treatment of cUTIs in the outpatient setting. ETX0282CPDP is a combination of ETX0282, a novel oral BLI, with cefpodoxime proxetil, or cefpodoxime, an oral β-lactam antibiotic. We believe ETX0282 is a highly differentiated oral β-lactamase inhibitor based on its broad inhibition of both Class A and Class C β-lactamases. We selected cefpodoxime as the β-lactam antibiotic to combine with ETX0282 following *in vitro* studies in which cefpodoxime exhibited superior activity against multidrug-resistant *Enterobacteriaceae* compared to other existing oral β-lactams. Cefpodoxime was once used to treat cUTIs, among other indications, but its clinical utility is currently limited by β-lactamase-mediated resistance. We believe ETX0282 has the potential to restore the efficacy of cefpodoxime against multidrug-resistant *Enterobacteriaceae*. We have reported initial Phase 1 results, which indicate ETX0282 is generally safe and well tolerated and supports further progression. Having successfully completed the initial Phase 1 studies and preclinical work to deliver a formulation with the desired extended release profile, we now are seeking a partner to help further advance ETX0282CPDP through additional clinical trials.

Urinary Tract Infections

A urinary tract infection, or UTI, diagnosis can be classified as either uncomplicated or complicated. Uncomplicated UTI is an infection of one or more parts of the urinary tract system such as the kidneys, ureters, bladder or urethra with symptoms confined to the lower urinary tract and is often treated with generic oral antibiotics in the community setting. Uncomplicated UTIs, if left unresolved, can have serious consequences, including life-threatening kidney infections. cUTIs, including pyelonephritis, occur in a urinary tract that has metabolic, functional, or structural abnormality and include patients with comorbidities or patients with bladder catheters. These factors contribute to decreased resolution of such infections and therefore frequently require hospital-based therapy. ETX0282CPDP is designed to treat cUTIs, including those caused by multi-drug resistant *Enterobacteriaceae*, including some carbapenem-resistant strains, or CRE. *Enterobacteriaceae* species cause approximately 85% of all UTIs, of which *E. coli* is the most common pathogen, causing approximately 75% of infections. In addition, *Klebsiella* and *Pseudomonas* are also relatively common UTI pathogens. The emergence of multidrug-resistant bacteria has reduced the efficacy of commonly used oral antibiotics such as levofloxacin and ciprofloxacin, both fluoroquinolones, and trimethoprim/sulfamethoxazole. In the United States, over 30% of UTIs caused by *E. coli* and 10% of UTIs caused by *Klebsiella* are resistant to fluoroquinolones.

Market Opportunity

Patients with UTIs caused by bacteria resistant to existing oral treatment options frequently require hospital admission for treatment with IV antibiotics, even when they are otherwise healthy and fit to be treated outside the hospital setting. In the United States, it is currently estimated that between 3 and 4 million UTIs are treated in the hospital per year. Hospital admission not only leads to inconvenience for the patient and high treatment cost for the healthcare system, but it also increases the risk of transmitting drug-resistant bacterial strains to other hospitalized patients and potentially exposing UTI patients to other, more serious hospital-acquired infections. There are currently no effective oral treatments available for cUTIs, including those caused by multi-drug resistant *Enterobacteriaceae*. If approved, we believe ETX0282CPDP will provide clinicians a convenient, oral option to treat patients suffering from cUTIs caused by these multidrug-resistant pathogens, which could reduce the need for hospital or outpatient IV treatment of these infections. There is also an opportunity for ETX0282CPDP to facilitate early hospital discharge following a short course of IV antibiotics.

Clinical Development Plan

Phase 1 clinical trial: We conducted a multi-part Phase 1 clinical trial of ETX0282 in Australia and initial data readout in June 2019. The Phase 1 clinical trial was a randomized, double-blind and placebo-controlled study of ETX0282 alone, not in conjunction with CPDP and was designed to investigate safety, pharmacokinetics, drug-drug interactions and food effect in 99 healthy volunteers enrolled in 12 cohorts. The completed cohorts were; Part A: single-ascending dose escalation, fasted; Part B: food effect: fasted versus high fat meal; Part C: multiple dose with regular meals; Part D: drug-drug interaction with regular meals; and Part G: simulation of a high-fat PK profile (fasted).

Overall, the key findings were that ETX0282 was found to be generally safe and well tolerated, no significant adverse events were reported. ETX0282, as the prodrug, was rapidly converted to ETX1317, the active form of the drug, at all doses. Plasma concentrations were in therapeutic range and the conversion of ETX0282 to ETX1317 was not impacted by multiple dosing and with minimal accumulation. No drug-drug interactions were observed with cefpodoxime. 11 out of 77 subjects receiving ETX0282 experienced mild to moderate emesis (vomiting). The trial data indicated that emesis may be ameliorated by dosing with a high fat meal (not a normal diet). When ETX0282 was dosed in fasted healthy volunteers in a manner to mimic the PK of the high fat meal plus ETX0282 (Part G), no emesis was observed. Having reported preliminary Phase 1 trial results, we are now seeking a partner to help further advance ETX0282CPDP through additional clinical trials.

Competition

We initially designed ETX0282CPDP for the potential oral treatment of cUTIs in the outpatient setting. There are a variety of generically available antibiotic classes with limited utility available for the treatment of such infections, including cephalosporins, carbapenems and fluoroquinolones. Additionally, there are several approved IV branded agents targeting multidrug-resistant cUTIs, including Avycaz®, Vabomere®, Zemdri®, as well as the more recently approved IV products Fetroja® (Shionogi & Co., Ltd) and Recarbrio® (Merck & Co., Inc.). We are aware of additional potentially competitive oral product candidates that may address a limited breadth of multidrug-resistant Gram-negative pathogens including tebipenem from Spero Therapeutics Inc., which completed a Phase 3 clinical trial and filed an NDA submission to the FDA in the fourth quarter of 2021. Sulopenem, from Iterum Therapeutics Limited, has completed Phase 3 clinical trials and in the third quarter of 2021 received a Complete Response Letter, or CRL, from the FDA requesting additional data to support approval of oral sulopenem for the treatment of adult women with uncomplicated UTIs. Additional potentially competing programs in clinical development are Venatorx Pharmaceuticals' Phase 1 VRX-7145, an orally bioavailable beta-lactamase inhibitor (BLI) in a fixed combination with the third generation orally bioavailable cephalosporin, ceftibuten. Initial Phase 1 data on VRX-7145 was announced in July 2021. Qpex Biopharma Inc. has announced the initiation of Phase 1 studies of ORAvance™, an ultra-broad-spectrum oral beta-lactamase inhibitor for use in combination with beta-lactam antibiotics for drug-resistant gram-negative bacterial infections.

ETX0462

Overview

Leveraging our targeted-design platform, we have developed a potential new class of novel antibiotics that are non-β-lactam penicillin binding protein inhibitors which we are referring to as NBPs. In late 2019, we selected a new drug candidate from our NBP platform, ETX0462, a novel unsaturated diazabicyclooctane with antimicrobial activity against multiple Gram-negative pathogens including *Pseudomonas aeruginosa*, as well as a number of high-priority biothreat pathogens. If successful in development, we believe our NBPs would be the first, novel Gram-negative antibiotic class since the carbapenems were introduced in 1985. In collaboration with CARB-X, we are advancing this program through registration safety studies and pre-formulation development and there is an option for support into Phase 1 human studies upon successful completion of the ongoing studies.

Pseudomonas

Infections caused by multidrug-resistant *Pseudomonas* are some of the most difficult to treat bacterial infections today. Carbapenems and cephalosporins are commonly used to treat susceptible cases of *Pseudomonas.* However, in the United States, approximately 20% of *Pseudomonas* are resistant to both classes of antibiotics. Some recently approved antibiotics demonstrate improved efficacy against *Pseudomonas but* are still prone to multiple mechanisms of resistance. In many cases, the only treatment option for multidrug-resistant *Pseudomonas* is colistin or other antibiotics of the same class. While these antibiotics are potent in preclinical models, in practice, clinicians tend to reserve their use as last resort treatment options due to their toxicity in the kidney and nervous system, which limits dosing and, therefore, clinical efficacy.

Market Opportunity

Pseudomonas causes a variety of opportunistic infections, including intra-abdominal infections, surgical site infections, UTIs and nosocomial pneumonia. *Pseudomonas* is the most common Gram-negative pathogen associated with ventilator-acquired pneumonia. This is due in-part to the larger genome compared to other bacteria, which enables *Pseudomonas* to encode enzymes that metabolize, transport and efflux antibiotics. In addition, biofilm formation has been reported in the lungs of patients infected with *Pseudomonas*, which acts as a barrier preventing antibiotic access to the bacteria. *Pseudomonas* infections are on the rise with an estimated 600,000 to 750,000 cases occurring annually in the United States. In 2014, approximately 20% of *Pseudomonas* infections were resistant to each of carbapenems, cephalosporins and fluoroquinolones and 14% were resistant to at least three classes of antibiotics. We believe our novel class of NBPs, including ETX0462, has the potential to be used as monotherapy against infections caused by multidrug-resistant *Pseudomonas*.

Competition

We are initially developing ETX0462 for the treatment of infections caused by multidrug-resistant *Pseudomonas*. There are a variety of generically available antibiotic classes available for the treatment of antibiotic sensitive *Pseudomonas* infections, including cephalosporins, carbapenems and fluoroquinolones. However, there are fewer options for multidrug resistant *Pseudomonas*. Generic polymyxins like Colistin are often utilized in these infections, as are branded IV antibiotics including Avycaz® (Allergan Inc.), Zerbaxa®, and Recarbrio® (both from Merck & Co., Inc.) and Vabomere® (Melinta, Inc.). Cayston® (Gilead Inc.) is an inhaled antibiotic addressing *Pseudomonas* infections in the lungs of cystic fibrosis patients. Zerbaxa® and Cayston® are unfortunately not active when *Pseudomonas* expresses a carbapenemase enzyme but can potentially overcome other forms of resistance. The other three branded agents are BL/BLI combinations, and *Pseudomonas* has begun to develop resistance to this class of antibiotics via porin channel mutations or efflux pumps. We are aware of additional potentially competitive product candidates in clinical development that may address certain *Pseudomonas* infections including: Ftortiazinon, a small molecule in Phase 2 from the Gamaleya Research Institute (Russia); AR101, a monoclonal antibody in Phase 2 from Aridis Pharmaceuticals Inc.; AP-PA02, a Phase 1b/2 phage candidate from Armata Pharmaceuticals Inc.

Supply and Manufacturing

We do not own or operate manufacturing facilities to produce any of our product candidates, nor do we have plans to develop our own manufacturing operations in the foreseeable future. We currently rely on third-party contract manufacturers for our required raw materials, drug substance, and finished drug product for our preclinical research and clinical trials. Although we have contracts with these third parties to meet our current clinical supply needs, we do not have any current contractual relationships with these third parties for the manufacture of commercial supply of our product candidates after they are approved. As our product candidates approach potential approval by any regulatory agency, we intend to enter into agreements with third-party contract manufacturers for the commercial production of those products. We currently employ internal resources to manage our manufacturing vendor relationships and processes.

Government and Nonprofit Awards

Through December 31, 2021, we have received aggregate financial commitments of up to $24.4 million from the Trustees of Boston University through the CARB-X program, the U.S. Army Medical Research Acquisition Activity, a division of the U.S. Department of Defense, and NIAID in support of our ETX0282, ETX0462, NBP and discovery research programs. The CARB-X awards could provide up to a total of $18.5 million in funding and the NIH award could provide up to a total $15.5 million in funding based on the successful completion of prespecified milestones. These specified milestones include the completion of important steps for a development-stage project such as preclinical studies or clinical trials, manufacture and formulation work, submission of regulatory applications and regulatory meetings with the FDA or comparable foreign regulator.

COVID-19 Business Impact

The COVID-19 pandemic continues to impact the global economy and healthcare industry, causing disruptions to business operations, interruptions in supply chains, and crowding hospitals and other healthcare facilities. With regard to our operations ,the pandemic continues to impact our ongoing clinical trial for zoliflodacin as patients either avoid seeking treatment or fail to return for follow-up visits due to crowded healthcare facilities. Aside from this impact, the pandemic has had little to no impact on our employees, other research and development pipeline programs, our ability to communicate with and manage our key vendors, partners, and drug supply chains, and accurately and timely file our financial statements. Although we are continuing to actively monitor and assess the effects of the COVID-19 pandemic on our business and pipeline programs, the ultimate impact of the COVID-19 pandemic is highly uncertain and subject to change.

License and Collaboration Agreements

A significant part of our strategy is to partner with established pharmaceutical companies, as well as nonprofit organizations, government agencies and other third parties to provide financial and technical support in the development and marketing of our products.

Zai Lab

In April 2018, we entered into a license and collaboration agreement with Zai Lab for the development and commercialization of products containing durlobactam or SUL-DUR in the following countries in the Asia Pacific region: China, Hong Kong, Macau, Taiwan, Korea, Vietnam, Thailand, Cambodia, Laos, Malaysia, Indonesia, the Philippines, Singapore, Australia, New Zealand and Japan, which we refer to collectively as the territory. Under the agreement, we granted Zai Lab an exclusive, royalty-bearing license, with the right to sublicense, under our technology to develop, manufacture and sell products containing durlobactam or SUL-DUR, or the licensed products, in the territory. Additionally, we granted Zai Lab a non-exclusive, worldwide license to our technology as required for Zai Lab to practice its exclusive license with respect to the licensed products. We retain the right to use our technology to perform our obligations under the agreement and retain the exclusive right to use our technology in all other countries, including North America and Europe.

Under the agreement, Zai Lab will use commercially reasonable efforts to perform and fund costs associated with our ATTACK Phase 3 registration trial of SUL-DUR in China. Zai Lab is responsible, at its expense, for developing licensed products in the territory, to be coordinated with our continued global efforts with respect to products containing SUL-DUR. Zai Lab must use commercially reasonable efforts to conduct development activities described in the agreed-upon written development plan and to obtain regulatory approval in a specified number of countries in the territory beyond China after regulatory approval of a licensed product in China. Zai Lab is also solely responsible for commercializing licensed products in the territory and must use commercially reasonable efforts to commercialize licensed products for which it has obtained regulatory approval. We are also obligated to supply Zai Lab with the licensed products for clinical development, although Zai Lab may take over manufacturing responsibilities for its own commercialization activities within a specified time period following the effective date of the agreement. Both parties are prohibited from developing and commercializing products in the territory that would compete with the licensed products.

We received an upfront, non-refundable payment of $5.0 million, milestone payments of $7.0 million, research support funding of $0.6 million and certain other reimbursable registration trial costs of $5.4 million, less applicable taxes of $2.2 million from Zai Lab through December 31, 2021. We are eligible to receive up to an aggregate of $91.0 million in additional research and development support payments and development, regulatory and sales milestone payments related to SUL-DUR, imipenem and other combinations with the licensed products. Zai Lab will pay us a tiered royalty equal to a high-single digit to low-double digit percentage based on annual net sales of licensed products in the territory, subject to specified reductions for the market entry of competing products, loss of patent coverage of licensed products and for payments owed to third parties for additional rights necessary to commercialize licensed products in the territory.

Zai Lab may terminate the agreement upon written notice to us at any time and for any reason. Further, we can terminate the agreement if Zai Lab ceases to commercialize the licensed products or challenges any of the patents we licensed to it.

GARDP

In July 2017, we entered into a collaboration agreement with GARDP for the development and commercialization of a product candidate containing zoliflodacin in certain countries. Under the terms of the collaboration agreement, GARDP will use commercially reasonable endeavors to perform and fully fund the Phase 3 registration trial, including the manufacture and supply of the product candidate containing zoliflodacin, in uncomplicated gonorrhea. Both parties are responsible for obtaining marketing authorizations for any future product candidate in such parts of their respective territories as they elect.

In addition, under the collaboration agreement, we have granted GARDP a worldwide, fully paid, exclusive and royalty-free license, with the right to sublicense, to use our zoliflodacin technology in connection with GARDP's development, manufacture and commercialization of zoliflodacin in low-income and specified middle-income countries, which we refer to collectively as the GARDP territory. We have retained commercial rights in all other countries worldwide, including the major markets in North America, Europe and Asia-Pacific. We also have retained the right to use and grant licenses to our zoliflodacin technology to perform our obligations under the collaboration agreement and for any purpose other than gonorrhea or community-acquired indications. GARDP will own all intellectual property developed in its performance under the collaboration agreement regarding formulation development of zoliflodacin. In the event we undertake and fund additional efforts outside of the current agreed-upon development plan for zoliflodacin in our territory that leads to the creation of new intellectual property, we will have a right to file and maintain this new intellectual property. In addition, we are obligated to maintain the intellectual property in the countries in the GARDP territory where we filed patent rights at the date of the agreement and, under specified conditions, in our territory, and GARDP must reimburse us for costs and expenses for the maintenance of such intellectual property rights in the countries of the GARDP territory. If we believe the results of the Phase 3 registration trial of zoliflodacin would be supportive of an application for marketing approval, we are obligated to use our best efforts to file an application for marketing approval with the FDA within six months of the completion of the trial and to use commercially reasonable endeavors to file an application for marketing approval with the EMA. Each party is responsible for using commercially reasonable efforts to obtain marketing authorizations for the product candidate in their respective territories.

Both parties have the right to terminate the collaboration agreement with 90 days' written notice if the other party is in material breach or remains in material breach after a cure period, or with immediate effect upon the occurrence of certain specified events of insolvency. Either party may terminate the collaboration agreement at any time after completion or earlier termination of the Phase 3 registration trial with 12 months' prior notice. We may terminate the collaboration agreement if GARDP has not achieved certain clinical milestones within a specified time period, unless the nonachievement was due to specified types of delay.

AstraZeneca

In May 2015, we entered into a Business Transfer and Subscription Agreement, or the AstraZeneca Agreement, with AstraZeneca, AstraZeneca UK Limited and AstraZeneca Pharmaceuticals LP, which was amended and restated in March 2016 and further amended in August 2017, pursuant to which we obtained, among other things, worldwide rights to SUL-DUR, ETX0282 and zoliflodacin.

Pursuant to the terms of the AstraZeneca Agreement, we agreed to pay AstraZeneca a one-time milestone payment of $5.0 million within three months of achieving a specified cumulative net sales milestone for SUL-DUR. This milestone payment will be automatically waived should our common stock trade on Nasdaq at or above a specified price at the time we achieve such specified cumulative net sales milestone for SUL-DUR, subject to adjustment for share splits, dividends and other similar events. We are also obligated to pay AstraZeneca a one-time milestone payment of $10.0 million within two years of achieving the first commercial sale of zoliflodacin. If our board of directors deems the milestone payment obligation related to zoliflodacin to be significantly burdensome, AstraZeneca is required to explore in good faith, modifications to the timing of such payment. At our election, either milestone payment may be paid in cash, shares of our common stock, or a combination of cash and stock. Additionally, we are obligated to pay AstraZeneca tiered, single-digit royalties on the annual worldwide net sales of SUL-DUR and, and the lesser of tiered, single-digit royalties on the worldwide annual net sales of zoliflodacin and a specified share of the royalties we receive from sublicensees of zoliflodacin. Royalties on sales of zoliflodacin do not include sales by GARDP in low-income and select middle-income countries. Our obligation to make these royalty payments expires with respect to each product on a country-by-country basis upon the later of (i) the 10 year anniversary of the first commercial sale of a product in each such country or (ii) when the last patent right covering a product expires in each such country.

See Note 9, *License and Collaboration Agreements*, and Note 14, *Commitments*, in the accompanying notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for more information on these collaborations and license agreements.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our product candidates, our core technologies, and other know-how. To accomplish this we rely on the skills, knowledge and experience of our scientific and technical personnel, as well as that of our advisors, consultants and other contractors. To help protect our proprietary know-how that is not patentable, we rely on trade secret protection and confidentiality agreements to protect our interests. We require our employees, consultants and advisors to enter into confidentiality agreements prohibiting the disclosure of confidential information and requiring disclosure and assignment to us of the ideas, developments, discoveries and inventions important to our business. We file patent applications directed to our key product candidates to establish intellectual property positions. These patent applications are intended to protect new chemical entities relating to these product candidates as well as their manufacturing processes, intermediates and uses in the treatment of diseases.

The intellectual property portfolios for our most advanced product candidates are summarized below.

Durlobactam

Our intellectual property portfolio for our durlobactam program contains patent applications directed to compositions of matter for durlobactam and other chemical analogs, as well as methods of making, referred to as synthetic methods, and methods of use and modes of treatment using durlobactam in combination with one or more antibiotic compounds. As of December 31, 2021, we owned four issued U.S. patents, one pending provisional application, 69 issued foreign patents as well as 12 pending foreign patent applications, of which two are allowed. The issued foreign patents are in several jurisdictions including Australia, the European Union, Canada, China, Hong Kong, Israel, India, Japan, Macau, Mexico, New Zealand, the Philippines, the Russian Federation, Singapore, South Africa, South Korea, Taiwan and the United Kingdom. Issued U.S. and foreign patents and patents issuing from pending U.S. and foreign applications will have expiration dates of April 2033 and November 2035.

Zoliflodacin

Our intellectual property portfolio for zoliflodacin contains patent applications directed to compositions of matter for zoliflodacin and other chemical analogs, as well as synthetic methods and methods of use and modes of treatment. As of December 31, 2021, we owned 7 issued U.S. patents, 71 issued foreign patents as well as six pending foreign patent applications. The issued foreign patents are in several jurisdictions, including Australia, Brazil, Canada, China, Eurasia, the European Union, Hong Kong, India, Israel, Japan, Mexico, New Zealand, Philippines, Singapore, South Africa, South Korea, Taiwan and the United Kingdom. Issued U.S. and foreign patents and patents issuing from pending U.S. and foreign applications have expiration dates of October 2029, January 2034 and May 2035.

ETX0282

Our intellectual property portfolio for our ETX0282 program contains patent applications directed to compositions of matter for the prodrug ETX0282, the active molecule, ETX1317, and other chemical analogs, as well as synthetic methods, and methods of use and modes of treatment using ETX0282 and ETX1317 in combination with one or more antibiotic compounds. As of December 31, 2021, we owned one issued U.S. patent, one pending U.S. application, two issued foreign patents, four allowed foreign patents and 15 pending foreign patent applications, of which one is allowed. Issued U.S. and foreign patents and patents issuing from pending U.S. and foreign applications will have expiration dates of September 2037.

ETX0462

Our intellectual property portfolio for our ETX0462 program contains patent applications directed to compositions of matter for ETX0462 and other chemical analogs, as well as synthetic methods, and methods of use and modes of treatment. As of December 31, 2021, we owned one granted U.S. patent application, one pending U.S. patent application, three issued foreign patents, and 17 pending foreign patent applications. Issued U.S. and foreign patents and patents issuing from pending U.S. and foreign applications will have expiration dates of May 2038.

Provisional Patents

In addition to the issued and pending patent applications covering our most advanced product candidates, our portfolio also includes one pending PCT application relating to an early stage discovery project.

Trademarks, Trade Secrets and Know-How

Our trademark portfolio currently consists of registered trademark and service mark rights for ENTASIS THERAPEUTICS in several jurisdictions, including the United States, the European Union, Japan, Argentina, Australia, Brazil, Canada, India, Mexico, Norway, the Russian Federation, South Korea, Switzerland, Taiwan, Turkey and the United Kingdom, and pending applications in other jurisdictions. In addition, we have registered trademark and service mark rights for ENTASIS THERAPEUTICS (plus design) in the United States, the European Union, Argentina, Brazil, Canada, Japan, Australia, India, Norway, the Russian Federation, South Korea, Switzerland, Taiwan, Turkey, Mexico and the United Kingdom, and pending applications in other jurisdictions. We have also registered trademark rights for XACDURO and XULDURO in the United States, the European Union, Brazil, China, Hong Kong, India, Macau, New Zealand, the Philippines, Taiwan, the United Arab Emirates, Argentina, Albania, Australia, Egypt, Macedonia, Mexico, Malaysia, Saudi Arabia, the United Kingdom, Belarus, Bosnia-Herzegovina, Cambodia, Indonesia, Israel, Laos, Japan, Moldova, Montenegro, Norway, the Russian Federation, Serbia, Singapore, South Korea, Switzerland, Turkey, Ukraine and Vietnam, and pending applications in other jurisdictions. In connection with the ongoing development and advancement of our products and services in the United States and various international jurisdictions, we routinely seek to create protection for our marks and enhance their value by pursuing trademarks and service marks where available and when appropriate. In addition to patents and trademark protection, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our commercial partners, collaborators, employees, and consultants, and invention assignment agreements with our employees. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed through a relationship with a third party. These agreements may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our commercial partners, collaborators, employees, and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

Government Regulation

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, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, import and export of our products and reimbursement. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulation require the expenditure of substantial time and financial resources.

U.S. Government Regulation

In the United States, the process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local statutes and regulations requires the expenditure of substantial time and financial resources. The failure to comply with the applicable 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 applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and untitled letters, product recalls, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement of profits or civil or criminal penalties.

Approval Processes

In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act, or the FDCA, the Public Health Service Act, or PHSA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulation require the expenditure of substantial time and financial resources. Failure to comply with the FDCA and other applicable U.S. requirements at any time during the product development process, approval process or after approval may subject us to a variety of administrative or judicial sanctions, any of which could have a material adverse effect on us. These sanctions could include:

- refusal to approve pending applications;
- withdrawal of an approval;
- imposition of a clinical hold;
- warning letters, untitled letters and similar communications;
- product seizures or recalls; or
- total or partial suspension of production or distribution, or injunctions, fines, restitution, disgorgement of profits or civil or criminal investigations and penalties brought by the FDA and the Department of Justice, or DOJ, or other governmental entities.

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 conducted according to Good Laboratory Practices or other applicable regulations;
- submission to the FDA of an IND application, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug for its intended use, conducted in accordance with current good clinical practices, or cGCP, which are ethical and scientific quality standards and FDA requirements for conducting, recording and reporting clinical trials to assure that the rights, safety and well-being of trial participants are protected;
- preparation and submission to the FDA of an NDA;

- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices, or cGMP, requirements to assure that the facilities, methods and controls are adequate to preserve the drug's safety, identity, strength, quality and purity; and

- FDA review and approval of the NDA.

Once a pharmaceutical candidate is identified for development, it enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND. Some preclinical or nonclinical testing may continue even after the IND is submitted. In addition to including the results of the preclinical studies, the IND will also include one or more protocols detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated if the first phase lends itself to an efficacy determination. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, places the IND on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. A clinical hold may occur at any time during the life of an IND and may affect one or more specific studies or all studies conducted under the IND.

All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with cGCP. They must be conducted under protocols detailing, among other things, the objectives of the trial, dosing procedures, subject selection and exclusion criteria and the safety and effectiveness criteria to be evaluated. Each protocol and any amendments must be submitted to the FDA as part of the IND, and progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently in other situations, including the occurrence of serious adverse events. An IRB at each institution participating in the clinical trial must review and approve the protocol and any amendments before a clinical trial commences or continues at that institution, approve the information regarding the clinical trial and the informed consent form that must be provided to each trial subject or his or her legal representative, monitor the study until completed and otherwise comply with IRB regulations. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health for public dissemination on their ClinicalTrials.gov website.

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

- Phase 1. The drug is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, distribution, metabolism and elimination. In the case of some products for severe or life-threatening diseases, such as multidrug-resistant infections, especially when the product may be inherently too toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients with the target disease or condition.

- Phase 2. Clinical trials are initiated in a limited patient population intended to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

- Phase 3. Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical study sites. These studies are intended to establish the overall risk-benefit ratio of the product and provide an adequate basis for regulatory approval and product labeling.

Phase 1, Phase 2 and Phase 3 testing may not be completed successfully within any specified period, if at all. The FDA or the sponsor may suspend or terminate a clinical trial at any time for a variety of reasons, including a finding that the research subjects or patients 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.

During the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points, including prior to submission of an IND, at the end of Phase 2 and before an NDA is submitted. Meetings at other times may also be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date, for the FDA to provide advice and for the sponsor and the FDA to reach agreement on the next phase of development. Sponsors typically use the end-of-Phase 2 meeting to discuss their Phase 2 clinical results and present their plans for the pivotal Phase 3 clinical trial or trials that they believe will support approval of the new drug.

The Pediatric Research Equity Act, or PREA, requires a sponsor to conduct pediatric studies for certain drugs and biologics. Specifically, PREA requires original NDAs, biologic license applications, or BLAs, and supplements thereto for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration to contain a pediatric assessment unless the sponsor has received a deferral or waiver.

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

The results of product development, preclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. The submission of an NDA is subject to the payment of user fees, but a waiver of such fees may be obtained under specified circumstances. The FDA reviews all NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing. It may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to completeness review before the FDA accepts it for filing.

Once the submission is accepted for filing, the FDA begins an in-depth review. NDAs receive either standard or priority review. A drug that, if approved, would represent a significant improvement in the safety or effectiveness of the treatment, prevention or diagnosis of a serious disease or condition may receive priority review. Requests for priority review generally must be submitted at the time of NDA submission. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of new molecular entities, or NMEs, are meant to be reviewed within ten months from the date on which FDA accepts the NDA for filing, and 90% of applications for NMEs that have been designated for "priority review" are meant to be reviewed within six months of the filing date. For applications seeking approval of drugs that are not NMEs, the ten-month and six-month review periods run from the date that FDA receives the application. The review process may be extended by the FDA for three additional months to consider a major amendment to the application following the original submission.

The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing complies with cGMP requirements to assure and preserve the product's safety, identity, strength, quality and purity. The FDA may refer the NDA to an advisory committee for review and recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendation.

Before approving an NDA, the FDA will typically inspect the facility or facilities where the product is manufactured and tested. These pre-approval inspections may cover all facilities associated with NDA submission, including drug component manufacturing (such as active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with cGCP. In addition, the FDA may require, as a condition of approval, risk evaluation and mitigation strategies, or REMS (which may include requirements for, restricted distribution and use), enhanced labeling, special packaging or labeling, expedited reporting of certain adverse events, pre-approval of promotional materials, restrictions on direct-to-consumer advertising or commitments to conduct additional research post-approval.

On the basis of the FDA's evaluation of the NDA and accompanying information, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. If the FDA ultimately decides that the NDA does not satisfy the criteria for approval, the FDA will issue a complete response letter to indicate that the agency will not approve the NDA in its present form. The complete response letter usually describes all of the specific deficiencies in the NDA identified by the FDA. If a complete response letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application.

Expedited Review and Approval

The FDA has various programs, including Fast Track and priority review, which are intended to expedite or simplify the process for developing and/or reviewing drugs. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification or that the time period for FDA review or approval will not be shortened. Generally, drugs that may be eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs and those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to facilitate the clinical development and expedite the review of drugs to treat serious diseases with the potential, based on nonclinical or clinical data, to fill an unmet medical need. Priority review is designed to give drugs that offer a significant improvement in safety or effectiveness of treatment for a serious condition an expedited review within eight months from the completed submission (six months from filing) as compared to a standard review time of twelve months from the completed submission (10 months from filing) for a standard new molecular entity NDA. Although Fast Track and priority review do not affect the standards for approval, the FDA will attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug and expedite review of the application for a drug designated for priority review.

The Generating Antibiotic Incentives Now Act, or GAIN Act, is intended to provide incentives for the development of new QIDPs. A new drug that is designated as a QIDP after a request by the sponsor that is made before an NDA is submitted will be eligible, if approved, for an additional five years of exclusivity beyond any period of exclusivity to which it would have previously been eligible. In addition, a QIDP will receive priority review and qualify for a Fast Track designation. QIDPs are defined as antibacterial or antifungal drugs intended to treat serious or life-threatening infections, including those caused by an antibacterial or antifungal resistant pathogen or qualifying pathogens identified by the FDA. SUL-DUR has been designated by the FDA as a QIDP for the treatment of hospital-acquired and ventilator-acquired bacterial pneumonia and bloodstream infections due to *A. baumannii*. Zoliflodacin has also been designated as a QIDP by the FDA for the treatment of uncomplicated gonorrhea.

Patent Term Restoration and Data Exclusivity

Depending upon the timing, duration and specifics of FDA approval of the use of our drugs, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. As noted above, the Hatch-Waxman Amendments permit a patent restoration term of up to five years for a single patent for an approved product as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date and only those claims covering such approved drug product, a method for using it or a method for manufacturing it may be extended. Only one patent applicable to an approved drug is eligible for the extension and the application for the

extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restoration of patent term for our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

Data exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications. 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 action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company using the drug entitled to data exclusivity as the reference listed drug, or RLD. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of data exclusivity for an NDA, 505(b)(2) NDA or supplement to an existing 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, for example, for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the use or conditions of use associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent for other uses or conditions of use. 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 its own preclinical and clinical studies in support of its application 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.

In addition, as described above, under the GAIN Act a new drug that is designated as a QIDP is eligible for an additional five years of exclusivity to be added to certain other exclusivity periods that the application may qualify for upon approval, specifically five-year exclusivity, three-year exclusivity, and orphan exclusivity.

Pediatric Exclusivity

The Best Pharmaceuticals for Children Act provides for an additional six months of exclusivity, which is added on to patent and exclusivity periods in effect at the time the pediatric exclusivity award is granted, if a sponsor conducts clinical trials in children in response to a written request from the FDA, or a Written Request. The FDA may request studies on approved indications in separate Written Requests. The issuance of a Written Request does not require the sponsor to undertake the described studies. To date, we have not received any Written Requests.

Post-approval Requirements

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, including safety issues, with a product may result in restrictions on the product or even complete withdrawal of the product from the market. 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 FDA review and approval. In addition, the FDA may require testing and surveillance programs to monitor the effect of approved products that have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs. The FDA and other authorities also strictly regulate the promotional claims that may be made about prescription products. Under the FDCA the sponsor of an approved drug in the United States may not promote that drug for unapproved, or off-label, uses, although a physician may prescribe a drug for an off-label use in accordance with the practice of medicine. If we are found to have promoted off-label uses, we may be subject to significant liability, including sanctions, civil and criminal fines and penalties, and injunctions prohibiting us from engaging in specified promotional conduct.

Moreover, any drug products manufactured or distributed pursuant to FDA approvals are subject to continuing regulation by the FDA, including, among other things:

- record-keeping requirements;
- reporting of adverse experiences with the drug;
- providing the FDA with updated safety and efficacy information;
- drug sampling and distribution requirements;
- notifying the FDA and gaining its approval of specified manufacturing or labeling changes;
- complying with certain electronic records and signature requirements; and
- complying with FDA promotion and advertising requirements.

Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and some state agencies for compliance with cGMP requirements and other laws.

Failure to comply with the FDCA and other applicable U.S. requirements at any time during the product development process, approval process or after approval may subject us to a variety of administrative or judicial sanctions, any of which could have a material adverse effect on us. These sanctions could include:

- refusal to approve pending applications;
- withdrawal of an approval;
- imposition of a clinical hold;
- warning letters, untitled letters and similar communications;
- product seizures or recalls;
- total or partial suspension of production or distribution; or
- injunctions, fines, restitution, disgorgement of profits or civil or criminal investigations and penalties brought by the FDA and DOJ, or other governmental entities.

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. In addition, FDA regulations and guidance are often revised or reinterpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether legislative changes will be enacted, or FDA regulations, guidance or interpretations changed or what the impact of such changes, if any, may be.

Foreign Regulation

In addition to regulations in the United States, we will be subject to a variety of foreign regulations governing clinical trials and commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of foreign countries or economic areas, such as the EU, before we may commence clinical trials or market products in those countries or areas. The approval process

and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

Under EU regulatory systems, a company may submit marketing authorization applications under the centralized, decentralized or mutual recognition procedures, or under the purely national route of approval. 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 acquired immune deficiency syndrome, or AIDS, cancer, neurodegenerative disorders, diabetes, viral diseases, and designated orphan medicines, and is optional for other medicines that are highly innovative. Under the centralized procedure, a marketing application is submitted to the European Medicines Agency, or EMA, where it will be evaluated by the relevant scientific committee, in most cases 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 EU member states and, by extension (after national implementing measures), in Norway, Iceland and Liechtenstein. In general, an initial marketing authorization is valid for five years, but once renewed is usually valid for an unlimited period. The decentralized procedure allows marketing authorization applications to be submitted simultaneously in two or more EU member states, whereas the mutual recognition procedure must be used if the product has already been authorized in at least one other EU member state. Both the decentralized and mutual recognition procedures provide 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 approve the assessment report and related materials, unless they identify a serious risk to public health. Under the mutual recognition procedure, the concerned member states have the same 90-day period to recognize the marketing authorization in the reference member state. In either case, concerns about serious risks to public health escalate through the relevant EMA scientific committees, and the disputed points may eventually result in a consensus opinion from the Committee for Medicinal Products for Human Use that is referred to the European Commission, whose decision is binding on all member states. The purely national procedure results in a marketing authorization in a single EU member state.

Following the result of a referendum in 2016, the United Kingdom left the EU on January 31, 2020, and as of January 1, 2021, the United Kingdom and EU operate separate regulatory regimes. The UK and EU announced on December 24, 2020, that they had agreed a Trade and Cooperation Agreement, or TCA, to govern their future relationship. The TCA remains provisional until formally ratified by the EU, which is expected to occur in early 2021. The TCA sets out the new arrangements for trade of goods, including medicines and medical devices, which aims to ensure goods continue to flow between the EU and the UK and also has implications for product regulation and mutual recognition.

As a result of the United Kingdom's departure from the EU, if a company wishes to sell its products in the United Kingdom, it will need to seek and maintain appropriate national marketing authorizations. The TCA does not provide for wholesale mutual recognition of the regulatory regimes and so products exported from the UK to the EU must comply with the EU's regulatory requirements. In the pharmaceutical context, this has had a number of implications. From January 31, 2020, the UK no longer participated in EU institutions and their decision-making, including approval decisions under the centralized procedure. Moreover, the movement of finished pharmaceutical products into the EU from the UK is treated as an import from a third country. Since the TCA does not provide for mutual recognition of batch testing and release, products must be quality control tested and released in the EU. However, the UK will unilaterally waive batch testing requirements for UK imports from the EU for products placed on the market before January 2023. It remains to be seen how these developments will impact regulatory requirements for product candidates and products in the United Kingdom.

Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such products. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all the approved products for a particular indication.

To secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies to demonstrate the medical necessity and cost effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. Additionally, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not ensure that other payors will also provide coverage for the drug product. Third-party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development.

Health Care Laws Governing Interactions with Healthcare Providers

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws restrict our business activities, including certain marketing practices. These laws include, without limitation, anti-kickback laws, false claims laws, data privacy and security laws, as well as transparency laws regarding payments or other items of value provided to healthcare providers.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item, good, facility or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers, among others, on the other. Although there are several statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration that are alleged to be intended to induce prescriptions, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the federal Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all its facts and circumstances. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the federal Anti-Kickback Statute has been violated. Additionally, the intent standard under the federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, collectively the Affordable Care Act, or ACA, to a stricter standard such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the ACA codified case law that a claim for payment for items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act.

Federal false claims laws, including the civil False Claims Act, and civil monetary penalties laws prohibit any person or entity from, among other things, knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a claim paid. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly inflating drug prices they report to pricing services, which in turn were 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, have also been alleged to violate false claims laws.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal and civil statutes that prohibit among other actions, knowingly and willfully 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 knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. As with the federal Anti-Kickback Statute, the ACA amended the intent standard for certain healthcare fraud under HIPAA such that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it to have committed a violation.

In addition, we may be subject to data privacy and security regulations promulgated by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, impose certain requirements on covered entities (i.e., certain healthcare providers, health plans and healthcare clearinghouses) relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards directly applicable to business associates, independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also created four 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 federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions.

Additionally, the federal Physician Payments Sunshine Act, created under the ACA, and its implementing regulations, require certain manufacturers of drugs, devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the children's health insurance program (with certain exceptions) to annually report information related to certain payments or other transfers of value provided to covered recipients, including physicians, as defined by such law, and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals' covered recipients and information related to certain ownership and investment interests held by physicians and their immediate family members.

Finally, the majority of states also have statutes or regulations similar to the aforementioned federal laws, some of which are broader in scope and apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government. In addition, some state laws require drug manufacturers to report information related to payments to clinicians and other healthcare providers or marketing expenditures and drug pricing. Further, some state and local laws require the licensure of pharmaceutical sales representatives. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Healthcare and Other Reform

In the United States, there have been and continue to be a number of significant legislative initiatives to contain healthcare costs. Federal and state governments continue to propose and pass legislation designed to reform delivery of, or payment for, healthcare, which include initiatives to reduce the cost of healthcare. For example, in March 2010, the United States Congress enacted the ACA, which expanded health care coverage through Medicaid expansion and the implementation of the individual mandate for health insurance coverage and which included changes to the coverage and reimbursement of drug products under government healthcare programs. Under the Trump administration, there were ongoing efforts to modify or repeal all or certain provisions of the ACA. For example, tax reform legislation was enacted at the end of 2017 that eliminated the tax penalty established under the ACA for individuals who do not maintain

mandated health insurance coverage beginning in 2019. The ACA has also been subject to judicial challenge. In December 2018, a federal district court, in a challenge brought by a number of state attorneys general, found the ACA unconstitutional in its entirety because, once Congress repealed the individual mandate provision, there was no longer a basis to rely on Congressional taxing authority to support enactment of the law. In December 2019, the federal appellate court upheld the district court ruling that the individual mandate was unconstitutional and remanded the case back to the district court to determine whether the remaining provisions of the ACA are invalid as well. The case has been appealed to the U.S. Supreme Court where a ruling remains pending.

There were other reform initiatives under the former Trump Administration, including initiatives focused on drug pricing. For example, the Bipartisan Budget Act of 2018 contained various provisions that affect coverage and reimbursement of drugs, including an increase in the discount that manufacturers of Medicare Part D brand name drugs must provide to Medicare Part D beneficiaries during the coverage gap from 50% to 70% starting in 2019. As another example, in 2018, President Trump and the Secretary of the HHS, released a "blueprint" to lower prescription drug prices and out-of-pocket costs. Certain proposals in the blueprint, and related drug pricing measures proposed since the blueprint, could cause significant operational and reimbursement changes for the pharmaceutical industry. HHS has solicited feedback on some of these measures and, at the same, has implemented others under its existing authority. On November 20, 2020, CMS issued an interim final rule through the CMS Innovation Center whereby Medicare Part B reimbursement for "certain high-cost prescriptions drugs" would be no more than most-favored-nation price (i.e., the lowest price) after adjustments, for a pharmaceutical product that the drug manufacturer sells in a member country of the Organization for Economic Cooperation and Development that has a comparable per-capita gross domestic product. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. While some of these and other measures may require additional authorization to become effective, members of Congress and the new Biden administration have indicated that lowering prescription drug prices is a priority, but it is not yet clear what steps the Biden Administration will take or whether such steps will be successful.

There have also been recent state legislative efforts to address drug costs, which generally have focused on increasing transparency around drug costs or limiting drug prices and address 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 2019, the DISARM Act of 2019 was introduced in Congress as new legislation to provide financial incentives for pharmaceutical companies to develop new antibiotics. This new legislation was guided by input from the IDSA and will help to ensure that patients can access new antibiotics when they are clinically appropriate, require hospitals to establish antibiotic stewardship programs, and spur improved reporting of antibiotic use and resistance to more rapidly identify challenges and inform best practices. More recently, this legislation was reintroduced in the U.S. House of Representatives in June 2021 which aims to amend title XVIII of the Social Security Act to encourage the development and use of DISARM antimicrobial drugs, and for other purposes.

General legislative cost control measures may also affect reimbursement for our product candidates. The Budget Control Act, as amended, resulted in the imposition of 2% reductions in Medicare, but not Medicaid, payments to providers in 2013 and will remain in effect through 2029 unless additional Congressional action is taken. There was a temporary suspension of the 2% reduction during the pandemic; that temporary suspension is scheduled to expire on March 31, 2021. Any significant spending reductions affecting Medicare, Medicaid or other publicly funded or subsidized health programs that may be implemented and/or any significant taxes or fees that may be imposed on us could have an adverse impact on our results of operations.

Legislation was introduced to the U.S. Senate in September 2020 which aims to reinvigorate innovation for the development of new antibiotics through a subscription contract program managed by HHS. The PASTEUR Act was introduced to provide a mechanism for funding designated 'critical need antimicrobial' drugs post FDA approval. In return, patients covered by federal insurance programs will receive these drugs at no cost. These Contracts under the PASTEUR Act could range from $750 million to $3 billion in value. It is unclear when or if the PASTEUR Act or similar incentive programs will become law. In October 2021, the PACCARB authored a letter to the Honorable Xavier

Becerra, Secretary, Department of Health and Human Services recommending the passage of both DISARM and PASTEUR and the antimicrobial stewardship provisions contained within each act.

Adoption of new legislation at the federal or state level could affect demand for, or pricing of, our current or future products if approved for sale. We cannot, however, predict the ultimate content, timing or effect of any changes to the ACA or other federal and state reform efforts. There is no assurance that federal or state health care reform will not adversely affect our future business and financial results.

Human Capital

As of December 31, 2021, we employed 51 people. We have no hourly employees. Thirteen of our employees work in our laboratory facilities while the remaining are office personnel. None of our employees are represented by a labor union or covered by a collective bargaining agreement.

The Human Resources Associate is responsible for developing and executing our human capital resources strategy. This includes the attraction, acquisition, development, engagement of talent and the design of employee compensation and benefits programs. The Chief Executive Officer regularly updates our board of directors and our committees on the operation and status of these human capital trends and activities.

Diversity, Equity and Inclusion

We have created an environment that fosters individual development while maintaining consistency in our corporate values and code of conduct. In 2020, we signed MassBio's Open Letter 2.0 – The CEO Pledge for a More Equitable & Inclusive Life Sciences Industry. By signing this Pledge, we are committing ourselves to take actions to foster a more diverse and inclusive environment in the life sciences industry. We continue to offer seminars from external consultants on diversity, equity and inclusion, or DEI, best practices and provide ongoing support to an internal discussion group focused on DEI topics important to the workplace.

Health, Safety and Wellness

We strive to provide pay, benefits and other employee services that are competitive to market in the life sciences industry and create incentives to attract and retain employees. Our compensation package includes market-competitive pay, stock options and restrictive stock units, bonuses, employee spot awards, health care and retirement benefits, paid time off and family leave. We utilize third party consultants to review and update our compensation practices annually. We are also committed to the continued development of its people, providing opportunities for employees to further their career development through internal training and education programs and third party online training programs. We have been certified as a “Great Place to Work” for the past three years and we believe our relationship with our employees to be good.

Corporate and Other Information

Entasis Therapeutics Holdings Inc. was incorporated under the laws of the State of Delaware in March 2018. Our shares are listed on The Nasdaq Global Market, where our trading symbol is ETTX. Our principal executive offices are located at 35 Gatehouse Drive, Waltham, Massachusetts 02451 and our telephone number is (781) 810-0120.

Entasis, the Entasis logo and other trademarks or service marks of Entasis Therapeutics Holding, Inc. appearing in this Annual Report on Form 10-K are the property of Entasis. This Annual Report on Form 10-K contains additional trade names, trademarks, and service marks of other companies. We do not intend our use or display of other companies’ trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us, by these other companies. Other trademarks appearing in this Annual Report on Form 10-K are the property of their respective holders.

Available Information

You may read our SEC filings, including our proxy statements, annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act, over the internet at the SEC's website at *www.sec.gov*. We also maintain a website at *www.entasistx.com*, at which you may access these materials free of charge as soon as reasonably practicable after they are electronically filed with, or furnished to, the SEC. The information contained in, or that can be accessed through, our website is not part of, and is not incorporated into, this Annual Report on Form 10-K.

Item 1A. Risk Factors

An investment in shares of our common stock involves a high degree of risk. You should carefully consider the following information about these material risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, including our financial statements and related notes hereto, before deciding to invest in our common stock. The occurrence of any of the following material risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this report and those we may make from time to time. In these circumstances, the market price of our common stock could decline; and you may lose all or part of your investment.

Risk Factor Summary

Risks Resulting from the Current Global Pandemic

- The COVID-19 pandemic has had, and may continue to have, an adverse effect on our business, development programs and access to capital.

Risks Related to Our Financial Position and Capital Needs

- We have incurred significant losses since our inception and we expect to incur losses over the next several years and may never achieve or maintain profitability.
- We require substantial additional funding to be able to continue as a going concern and, if we are unable to raise capital when needed, we could be forced to delay, reduce or altogether cease any regulatory, commercialization or product development efforts.
- Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.
- Provisions in the purchase agreement with Innoviva and related documents may deter or prevent us from raising additional capital to fund our operations.

Risks Related to the Development of Our Product Candidates and Preclinical Program

- We depend to a large degree on the success of our most advanced product candidates, one of which has completed a Phase 3 registrational trial. If we do not obtain regulatory approval for and successfully commercialize one or more of our product candidates or if we experience significant delays in doing so, we may never become profitable.
- If our current clinical trials for our product candidates, including the ATTACK trial, fail to demonstrate safety and efficacy to the satisfaction of the FDA, the EMA or other comparable 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 regulatory submissions of our product candidates.
- If we or our collaborators experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

Risks Related to Our Dependence on Third Parties

- We rely on third parties to conduct the clinical trials and support our NDA submission activities for our product candidates and those third parties may not perform satisfactorily.
- We rely on collaborations with third parties for the development of our product candidates, and we may seek additional collaborations in the future. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.
- Our reliance on third parties to manufacture and test our product candidates increases the risk that we will not have sufficient quantities or the required quality of our product candidates, not have our products available in a timely manner, or not have necessary quantities at an acceptable cost.
- Our reliance on government funding for certain of our programs adds uncertainty to our research and development efforts with respect to those programs and may impose requirements that increase the costs of the research and development of product candidates developed under those government-funded programs.

Risks Related to the Commercialization of Our Product Candidates

- If we are unable to establish sales, marketing, market access, manufacturing and distribution capabilities for our product candidates, or enter into sales, marketing, market access and distribution agreements with third parties, we may not be successful in commercializing our product candidates, if and when they are approved.
- Even if any of our product candidates receives marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

Risks Related to Our Business and Managing Our Growth

- We depend on the continuing efforts of our senior management team and other key personnel. If we lose members of our senior management team or other key personnel or are unable to successfully retain, recruit and train qualified researchers, engineering and other personnel, our ability to develop our products could be harmed, and we may be unable to achieve our goals.
- Significant disruptions to our information technology systems or data security incidents could result in significant financial, legal, regulatory, business and reputational harm to us.

Risks Related to Our Intellectual Property

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

Risks Related to Ownership of Our Common Stock

- Our largest shareholder, Innoviva, holds more than 50% of our common stock and, as a result, may exert a substantial influence on actions requiring stockholder vote, potentially in a manner that you do not support.
- The market price of our common stock is likely to be volatile and could fluctuate or decline, resulting in a substantial loss of your investment.
- The issuance of additional shares of stock, or actual or perceived sales by large holders, could depress the market price of our common stock.

- If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired, which would adversely affect our business.
- We have never paid dividends on our capital stock and we do not intend to pay dividends for the foreseeable future.

Risks Resulting from the Current Global Pandemic

The COVID-19 pandemic has had, and may continue to have, an adverse effect on our business, development programs and access to capital, and additional COVID-19 outbreaks may have a similar or worse impact on us.

The COVID-19 pandemic has had, and will continue to have, an unprecedented impact on the U.S. economy in general and large and small businesses in particular. Virus mutations have resulted in repeated surges in infection rates, resulting in disruptions to business operations as employers and workforces adapt to new working conditions and requirements. Since the onset of the pandemic, the majority of our employees have been working remotely and our laboratory workers have operated in reduced and/or staggered shifts. As regulatory agencies prioritize the review of therapies with the potential to minimize the extent and/or severity of the pandemic, review of regulatory submissions of other therapeutic products may experience delays. As healthcare systems focus on patients affected by the COVID-19 pandemic, global clinical trials, including our ongoing Phase 3 registration trial with zoliflodacin, have seen declines in activity or have been suspended temporarily. For instance, for the Phase 3 registration trial for zoliflodacin some clinical sites in high COVID-19 impact areas, have experienced periodic delays in new patient enrollment due to redirection of resources or hospital access restrictions as required by local conditions. GARDP, with our full agreement, had temporarily paused patient enrollment and activation of new clinical trial sites in March 2020. In June 2020, GARDP resumed patient enrollment into the Phase 3 registration trial at U.S. sites and ten new clinical trial sites were activated in the Netherlands (1), South Africa (5), Thailand (3) and the U.S. (1) during 2021. While we have not experienced material disruptions in our supply chain to date due to the COVID-19 pandemic, it may in the future impact our ability to procure resources, raw materials or components necessary for our development programs. For example, our contract manufacturing partners may see pandemic related disruptions, which could impede their ability to produce supply of our product candidates sufficient for further clinical testing and/or commercialization. As a result of the unpredictability surrounding the COVID-19 pandemic, the timelines for completion of our planned regulatory filing, registration trial and earlier-stage development programs may be materially impacted. Significant delays in the development of any of our product candidates will be costly and could adversely affect our ability to obtain regulatory approval for and successful commercialization of our product candidates. The nature and extent of the impact remains uncertain as the duration of the COVID-19 pandemic and the time needed for businesses and healthcare systems to recover remains unknown. Although we are continuing to actively monitor and assess the effects of the COVID-19 pandemic on our business and development programs, the ultimate impact of the COVID-19 pandemic is highly uncertain and subject to change.

Our ability to raise additional capital may be adversely impacted by worsening global economic conditions and the continuing disruptions to, and volatility in, financial markets in the United States and worldwide resulting from the ongoing COVID-19 pandemic. The continuation of prolonged adverse economic conditions (including due to a resurgence or subsequent waves of COVID-19 infections and delays in completing the distributions of COVID-19 vaccines) could limit our access to financial resources from the capital markets and other sources.

We are not yet certain about the full extent of the long-term potential impact of COVID-19 on our business, development programs and access to capital. To the extent COVID-19 continues to adversely affect our business, financial condition and results of operations, as well as global economic conditions more generally, it may also heighten many of the other risk factors described in this Annual Report on Form 10-K.

Risks Related to Our Financial Position and Capital Needs

We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

We are an advanced, clinical-stage, biopharmaceutical company with a limited operating history. We have not generated any revenue from the sale of products and have incurred losses in each year since our inception in 2015. Our net loss was $47.1 million and $50.5 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $231.6 million. We have funded our operations to date primarily with proceeds from the sale of common stock, warrants and convertible preferred stock. We have also either directly received funding or financial commitments from, or have had our program activities conducted and funded by, the U.S. government through our arrangements with the NIH, NIAID, CARB-X, and the DOD, and have received non-profit awards from GARDP, and upfront and milestone payments of $12.0 million, research support funding of $0.6 million and other reimbursable registration trial costs of $5.4 million, less applicable taxes, from our license and collaboration agreement with Zai Lab.

We have devoted substantially all of our financial resources and efforts to research and development, including preclinical studies and clinical trials. While we are advancing development of our product candidates, we have not completed development of any drugs. We expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially as we:

- continue our ongoing and planned preclinical and clinical development of our product candidates;
- initiate preclinical studies and clinical trials for any additional product candidates that we may pursue in the future;
- seek to discover and develop additional product candidates;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- consider establishing sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any product candidate for which we may obtain regulatory approval and intend to commercialize on our own;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, scientific, and chemistry, manufacturing and controls personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and
- incur additional legal, accounting and other expenses associated with operating as a commercial stage public company.

To become and remain profitable, we and our collaborators must succeed in developing and eventually commercializing drugs that generate significant revenue. This will require us, and in some cases our collaborators, to be successful in a range of challenging activities, including completing preclinical studies and clinical trials of our product

candidates, obtaining regulatory approval, manufacturing, marketing and selling any products for which we may obtain regulatory approval, as well as discovering and developing additional product candidates. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

Because of the numerous risks and uncertainties associated with drug development, we are unable to accurately predict the timing or amount of expenses or when, or if, we will be able to achieve profitability. If we are required by regulatory authorities to perform studies in addition to those currently completed or expected, or if there are any delays in the initiation and completion of our clinical trials, the submission or approval of our regulatory submissions, or the development of any of our product candidates, our expenses could increase.

Even if we achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our common stock and could impair our ability to raise capital, expand our business, maintain our research and development efforts or continue our operations. A decline in the value of our common stock could also cause you to lose all or part of your investment.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We commenced active operations in 2015, and our operations to date have been largely focused on raising capital, identifying and developing our product candidates and preclinical program, broadening our expertise in the development of our product candidates, and undertaking preclinical studies and conducting clinical trials. As an organization, we have not yet demonstrated an ability to successfully file an NDA and obtain regulatory approval, manufacture a commercial-scale product or arrange for a third party to do so on our behalf, or conduct, or secure a collaborator to conduct, sales and marketing activities necessary for successful commercialization. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

We expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

We require substantial additional funding to be able to continue as a going concern and to pursue our business objectives. If we are unable to raise capital when needed, we could be forced to delay, reduce or altogether cease our product development programs or commercialization efforts.

Absent any additional financing, our cash and cash equivalents as of December 31, 2021 together with the $15.0 million received in February 2022 from Innoviva as part of the securities purchase agreement, or the Fourth Securities Purchase Agreement, are expected to fund our operating expenses and capital expenditure requirements through the end of the third quarter of 2022 but are not sufficient to sustain our operations in the long term. As a result, our management has concluded that there is substantial doubt about our ability to continue as a going concern for the one-year period following the issuance of our financial statements for the year ended December 31, 2021. We will need to obtain substantial additional funding in connection with our continuing operations, which cannot be assured. Our future capital requirements will depend on many factors, including:

- the costs, timing and outcome of regulatory filings and review of our product candidates;
- the costs and timing of any potential commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;

- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the timing, progress and results of our ongoing clinical trials of our product candidates;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials of other product candidates that we may pursue;
- the number and development requirements of other product candidates that we may pursue;
- the amount of funding that we receive under our government awards and government awards that we have applied for;
- our ability to establish collaborations on favorable terms, if at all;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the costs of operating as a public company; and
- the extent to which we acquire or in-license other product candidates and technologies.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially available until at least 2023, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce the scope of, suspend or altogether cease our research and development programs or future commercialization efforts. We can provide no assurance that such actions would be adequate to sustain our operations in the long-term, and such actions may adversely affect our ability to grow in the future.

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

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt and/or royalty financings and potential collaboration, license and development agreements and government/non-profit grants and awards. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a stockholder. Debt or royalty 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.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to, or control of, our technologies, future revenue streams, research programs or product candidates or to 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 drug development or future commercialization efforts or grant rights to a third party to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Provisions in the Company's securities purchase agreement with Innoviva Inc. and related documents may make it more difficult for us to raise additional capital to fund our operations.

Provisions in the agreements we entered into in April 2020 in connection with the first private placement transaction, or the First Private Placement, may deter or prevent us from raising additional capital to fund our operations as and when needed. For example, the Investor Rights Agreement we entered into with Innoviva, or the Investor Rights Agreement, in connection with the First Private Placement provides participation rights for Innoviva to participate pro rata in our future offerings of securities. These and other provisions in the First Private Placement documents could deter or prevent us from raising additional capital. 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 pipeline and otherwise pursue our business strategy and we may be unable to continue as a going concern.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

As of December 31, 2021, we had U.S. federal and state net operating loss carryforwards, or NOLs, of $166.3 million and $167.4 million, respectively. We do not anticipate generating revenue from sales of products until 2023 at the earliest, if ever, and we may never achieve profitability. Unused NOLs generated in tax years ending on or prior to December 31, 2017 will carry forward for twenty years and, subject to the limitations as a result of an ownership change described below, will be available to offset future taxable income, if any, until they expire. Unused tax losses generated after December 31, 2017, will not expire and may be carried forward indefinitely, but will be deductible only to the extent of 80% of current taxable income in any given year (after deduction, if any of any pre-2018 NOLs). It is uncertain if and to what extent various U.S. states will conform to the U.S. federal income tax treatment of post-2017 NOLs.

Sections 382 and 383 of the U.S. Internal Revenue Code of 1986, as amended, which we refer to as the Code, provide additional limitations on the use of NOLs if a corporation undergoes an "ownership change." This is defined as a greater than 50 percentage point shift (by value) in the corporation's equity ownership by certain stockholders, generally over a three-year period. After an ownership change, a corporation's ability to use its pre-change NOLs and other pre-change tax attributes to offset its post-change taxable income or tax liabilities, both as determined for U.S. federal income tax purposes, is limited. We have experienced ownership changes in the past, and we may experience further ownership changes in the future as a result of future shifts in our share ownership, some of which shifts are outside our control. Accordingly, our ability to use our pre-change NOLs to offset taxable income, as determined for U.S. federal income tax purposes, may be subject to limitations. Similar limitations under U.S. state tax law may also apply to our use of accumulated state tax attributes, including our state NOLs. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. As a result, even if we attain profitability, we may be unable to use a material portion of our NOLs and other tax attributes, which could negatively impact our future cash flows.

Risks Related to the Development of Our Product Candidates and Preclinical Program

We depend to a large degree on the success of our most advanced product candidates, which remain in clinical development and for which we have not yet successfully submitted an NDA. If we do not successfully complete our clinical trials, submit our NDA or obtain regulatory approval for and successfully generate revenue from one or more of our product candidates or if we experience significant delays in doing so, we may never become profitable.

We currently have no products approved for sale and have invested a significant portion of our efforts and financial resources on the development of our product candidates for the treatment of serious infections caused by multidrug-resistant Gram-negative bacteria. We expect that a substantial portion of our efforts and expenses over the next few years will be devoted to the submission of applications for marketing authorization and potential FDA approval of SUL-DUR as well as development of our current product candidates. As a result, our business currently depends heavily on the successful development, regulatory approval and, if approved, commercialization of our product candidates. We cannot be certain that our product candidates will receive regulatory approval or will be successfully commercialized even if they receive regulatory approval. The research, development, manufacturing, safety, efficacy, labeling, approval, sale, marketing and distribution of our product candidates are, and will remain, subject to comprehensive regulation by the FDA, the EMA, and comparable foreign regulatory authorities. Before obtaining

regulatory approvals for the commercial sale of any product candidate, we must demonstrate through preclinical studies and clinical trials that the product candidate is safe and effective for use in each target indication. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of any of our clinical trials. Failure to obtain regulatory approval for our product candidates in the United States will prevent commercialization and marketing of our product candidates. The success of our product candidates and preclinical programs will depend on several additional factors, including:

- successful completion of preclinical studies and requisite clinical trials;
- performing preclinical studies and clinical trials in compliance with the FDA, the EMA or any comparable regulatory authority requirements;
- successful regulatory submissions and receipt of marketing approvals from applicable regulatory authorities;
- the ability of collaborators to manufacture sufficient quantity of product for development, clinical trials or potential commercialization;
- obtaining marketing approvals with labeling for sufficiently broad patient populations and indications, without unduly restrictive distribution limitations or safety warnings, such as black box warnings or a REMS, program;
- obtaining and maintaining patent, trademark and trade secret protection, and regulatory exclusivity for our product candidates and preclinical program;
- making arrangements with third parties for manufacturing capabilities;
- launching commercial sales of products, if and when approved, whether alone or in collaboration with others;
- acceptance of the therapies, if and when approved, by patients, physicians and third-party payors;
- competing effectively with other therapies;
- obtaining and maintaining adequate reimbursement for the therapies;
- protecting our rights in our intellectual property portfolio; and
- maintaining a continued acceptable safety profile of our drugs following approval.

If we do not achieve one or more of these factors in a timely manner or at all, our product candidates could experience significant delays to market or result in unsuccessful commercialization which would harm our business. If we do not successfully develop and commercialize product candidates or collaborate with others to do so, we will not be able to obtain product revenue in future periods, which could significantly harm our financial position and adversely affect the trading price of our common stock.

Success in preclinical studies or clinical trials may not be indicative of results in current or future clinical trials.

Success in preclinical testing and early clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. Our product candidates may fail to show the necessary safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through initial clinical trials.

In addition, the design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. As an organization, we have limited experience designing clinical trials and may be unable to design and execute a clinical trial to support regulatory approval. There is a high failure rate for drugs and biologic products proceeding through clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections because of many factors, including changes in regulatory policy during the period of our product candidate development. Any such delays could negatively impact our business, financial condition, results of operations and prospects.

If clinical trials of any of our product candidates fail to demonstrate safety and efficacy to the satisfaction of the FDA, the EMA or other comparable 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 that product candidate.

We, or our potential collaborates, may not commercialize, market, promote, or sell any product candidate without obtaining marketing approval from the FDA, the EMA or other comparable regulatory authority, and we may never receive such approvals. Even if our product candidates appear sufficiently effective and/or safe in patients in well-controlled clinical trials, it is impossible to predict if or when these product candidates will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any product candidate, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

We may experience numerous unforeseen events prior to, during, or because of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- the FDA, the EMA or other comparable regulatory authority may change from the views they have expressed to us as to the design, implementation, and/or interpretation of our clinical trials;
- the FDA may withdraw Fast Track designation if it believes that the designation is no longer supported by data from our clinical development program;
- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may not reach agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- clinical trials of our product candidates may produce negative or inconclusive results; for example, the clinical cure rate of patients with uncomplicated gonorrhea treated with intermuscular ceftriaxone is high, which may confound the analysis of the zoliflodacin Phase 3 registration trial;
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- we may not be able to complete our clinical trials in a timely manner, if at all, for example because the number of patients required for clinical trials of our product candidates may be larger than we anticipate,

enrollment in these clinical trials may be slower than we anticipate, participants may drop out of these clinical trials at a higher rate than we anticipate, or we may fail to recruit suitable patients to participate in a trial;

- we may fail to comply with regulatory requirements applicable to us to FDA's or other comparable regulatory authority's satisfaction;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- regulators may issue a clinical hold, or regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the FDA, the EMA or other comparable regulatory authorities may fail to approve the manufacturing processes or facilities of third-party manufacturers with whom we enter into agreements for clinical and commercial supplies;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- our product candidates, once exposed to greater numbers of patients, may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the clinical trials or cause regulatory authorities to refuse to approve our product candidates or approve them only with significant restrictions on distribution or use;
- even if our clinical trials are successful, the FDA, the EMA or other comparable regulatory authorities may determine that the overall risk-benefit profiles of our product candidates are insufficient to support marketing authorization; and
- the approval policies or regulations of the FDA, the EMA or other comparable regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

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

- be delayed in obtaining 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 safety warnings, such as black box warnings or a REMS program;
- be subject to additional post-marketing testing requirements; or
- be required to remove the product from the market after obtaining marketing approval.

Our product development costs may also increase if we experience delays in testing and we may be required to obtain additional funds to complete clinical trials. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant preclinical study or 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. 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 a product candidate.

If we are not successful in discovering, developing, and commercializing additional product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.

Although a substantial amount of our effort will focus on the continued clinical testing and potential regulatory approval of our product candidates, an element of our strategy is to develop and commercialize, either by ourselves or with a collaborator, our highly differentiated, targeted product candidates to treat serious infections caused by multidrug-resistant Gram-negative bacteria and discover and develop novel product candidates in other therapeutic areas. We are seeking to do so by utilizing our discovery research experience and capabilities to design active new compounds that target causative mechanisms of disease. To date we have focused our clinical development on multidrug-resistant pathogens and plan to leverage this experience in the development and regulatory paths available for first-in-class or best-in-class molecules in other therapeutic areas. Research efforts to identify and develop product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for many reasons, including the following:

- the research methodology used may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render our product candidates obsolete or less attractive;
- product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- a product candidate may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all;
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors, if applicable; and
- the FDA, the EMA or other regulatory authorities may not approve or agree with the intended use of a new product candidate.

If we fail to develop and successfully generate revenue from other current and future product candidates, our business and future prospects may be harmed, and our business will be more vulnerable to any problems that we or potential collaborates may encounter in developing and commercializing our current product candidates.

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

We may not be able to initiate, continue or complete clinical trials of our product candidates that we develop if we and our collaborators are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA, the EMA or other comparable regulatory authority. We have limited experience enrolling patients in our clinical trials and cannot predict how successful we will be in enrolling patients in future clinical trials.

For instance, patients involved in our clinical trials are generally in the hospital setting and the decision to participate can be made by the caregiver or doctor. Accordingly, seeking consent for patient participation may become difficult when the family and/or the patient may not be available to consider participation in a clinical trial and the providers/investigators seeking the consent often have no established relationship with the family or patient. The challenges of obtaining consent for patient participation have increased during the COVID-19 pandemic as hospitals have imposed restrictions on visitation by friends or family members who may be able to provide consent on behalf of patients. The COVID-19 pandemic may make patients less willing to seek medical attention or return for follow-up visits post-treatment. In addition, some of our competitors have ongoing clinical trials to treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors. If we are not successful at enrolling patients in one clinical trial, it may affect when we are able to initiate our next clinical trial, which could result in significant delays in our efforts to pursue regulatory approval of and commercialize our product candidates. Patient enrollment is affected by other factors including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the proximity and availability of clinical trial sites for prospective patients;
- the eligibility criteria for participation in the clinical trial;
- the design of the clinical trial;
- the perceived risks and benefits of the product candidate under study;
- our ability to recruit clinical trial investigators with appropriate experience;
- the availability of drugs approved to treat the diseases under study;
- the patient referral practices of physicians;
- our ability to obtain and maintain patient consents;
- the ability to monitor patients adequately during and after treatment;
- the risk that patients enrolled in clinical trials will drop out of the trials before completion; and
- the impact of public health epidemics, such as the COVID-19 pandemic.

Our inability to enroll a sufficient number of patients for clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in these clinical trials may result in increased development costs for our product candidates, which would reduce the capital we have available to support our current and future product candidates and may result in our need to raise additional capital earlier than planned and could cause the value of our common stock to decline and limit our ability to obtain additional financing.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval.

During the conduct of clinical trials, patients report changes in their health, including illnesses, injuries and discomforts (generally referred to as adverse events), to their doctor. We are required to report adverse events to the FDA and other regulatory authorities. Often, it is not possible to determine whether the product candidate being studied caused these conditions. Regulatory authorities may draw different conclusions or require additional testing to confirm

or refute these observations, if they occur. In addition, it is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of these product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by subjects. Many times, side effects are only detectable after investigational drugs are tested in large-scale, Phase 3 clinical trials or, in some cases, after they are made available to patients on a commercial scale after approval. If additional clinical experience indicates that any of our current product candidates or any future product candidates of ours, has side effects or causes serious or life-threatening side effects, the development of the product candidate may fail or be delayed, or, if the product candidate has received regulatory approval, such approval may be revoked, which would harm our business, prospects, operating results and financial condition.

Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of our product candidates, the commercial prospects of our product candidates may be harmed and our ability to generate revenue through their sale may be delayed or eliminated. Any of these occurrences may significantly harm our business, financial condition and prospects.

Additionally, if any of our product candidates receive marketing approval, regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication, or the adoption of a REMS program to ensure that the benefits outweigh its risks, which may include, among other things, a medication guide outlining the risks of the drug for distribution to patients and a communication plan to health care practitioners, and/or significant restrictions on distribution or use of the drug. Furthermore, if we or others later identify undesirable side effects caused by our product candidates, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product candidate;
- regulatory authorities may require additional warnings on the label or impose distribution or use restrictions;
- we may be required to change the way a product candidate is administered or conduct additional clinical trials, including one or more post-market studies;
- we could be sued and held liable for harm caused to patients;
- we may be required to implement a REMS, including the creation of a medication guide outlining the risks of such side effects for distribution to patients, and/or other elements to assure safe use;
- we may need to conduct a recall; 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.

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 have a greater likelihood of success.

Because we have limited financial and management resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs 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 products. 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 such product candidate.

Interim "top-line" and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may announce interim top-line or preliminary data from our clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and/or more patient data become available. Preliminary or top-line data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Differences between preliminary or interim data and final data could significantly harm our business prospects and may cause the trading price of our common stock to fluctuate significantly.

Two of our product candidates are β-lactamase inhibitors developed in combination with approved β-lactam antibiotics. If the FDA, the EMA or a comparable regulatory authority revokes the approval of one or both of β-lactam antibiotics, we may be unable to obtain approval for our product candidates.

Two of our product candidates inhibit one of the most prevalent forms of bacterial resistance, β-lactamase enzymes, so-named because of their ability to inactivate β-lactam antibiotics, one of the most commonly used classes of antibiotics. By blocking this resistance mechanism, these product candidates, when administered in combination with β-lactam antibiotics, are designed to restore the efficacy of those antibiotics. Durlobactam is a novel IV, broad-spectrum BLI that we are developing in combination with sulbactam, an IV β-lactam antibiotic, for the treatment of a variety of serious multidrug-resistant infections caused by *Acinetobacter*. ETX0282 is a novel, oral BLI that we are developing in combination with cefpodoxime, an oral β-lactam antibiotic, for the treatment of cUTIs, including those caused by *Enterobacteriaceae*.

Sulbactam and cefpodoxime are both FDA approved antibiotics. However, we did not develop or obtain marketing approval for, nor do we manufacture or sell, sulbactam or cefpodoxime or any other currently approved drug that we may study in combination with our product candidates. If the FDA, the EMA or a comparable regulatory authority revokes the approval of the drug or drugs in combination with which we determine to develop our product candidates, we may not be able to market our product candidates in such jurisdictions.

Furthermore, if safety or efficacy issues arise with any of these drugs, we could experience significant regulatory delays, and the FDA, the EMA or a comparable regulatory authority may require us to redesign or terminate the applicable clinical trials. In addition, if manufacturing or other issues result in a shortage of supply of the drugs with which we determine to combine with our product candidates, we may not be able to complete their clinical development on our current timeline or at all.

Even if our product candidates were to receive marketing approval or be commercialized for use in combination with other existing drugs, we would continue to be subject to the risks that the FDA, the EMA or a comparable regulatory authority could revoke approval of the drug used in combination with our product candidates or that safety, efficacy, manufacturing or supply issues could arise with these existing drugs.

Demand for our product candidates, if approved, will depend in part on continued resistance to empirically used broad-spectrum antibiotics and continued use of pathogen identification and resistance profiling.

Each of our product candidates, is aimed at treating antibiotic resistant gram-negative bacteria of a specific genus and/or species, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* or certain strains of *Enterobacteriaceae*. Typically, when a patient presents with an infection and the bacteria causing the infection is not known or only suspected, a broad-spectrum antibiotic is administered as a first-line empiric treatment pending tests to identify the bacterial pathogen causing the infection and resistance profile. Our product candidates are being developed

for use following the identification of the bacterial pathogen and if the resistance profile of the bacterial pathogen suggests that the first-line broad-spectrum antibiotic is not likely to be effective. Our product candidates are designed to treat specific antibiotic-resistant bacteria where broad-spectrum antibiotics are typically not effective due to the development of antibiotic resistance. However, in those cases when empiric treatment with a broad-spectrum antibiotic has been effective, or in other words the bacteria remain susceptible to existing antibiotics, there would not be a need for treatment of drug-resistant bacteria with our product candidates. If the bacteria we target become less resistant to existing broad-spectrum antibiotics, or if new broad-spectrum antibiotics are developed that are equally effective against the specific bacteria we target, then the potential demand for our product candidates could be diminished.

In addition, while pathogen identification and resistance profiling are common tests that have been employed for decades and are standard practice in hospital microbiology laboratories, and as more recently developed and approved rapid diagnostic technologies have demonstrated utility to guide the appropriate use of antibiotics, both these approaches can be costly and/or time consuming. If these tests do not remain standard procedure and available for clinicians, for example because their coverage and reimbursement status by third-party payors is reduced or eliminated, this could also limit the potential demand for our product candidates.

Risks Related to Our Dependence on Third Parties

We rely on third parties to conduct the clinical trials for our product candidates, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials or failing to comply with applicable regulatory requirements.

We have engaged contract research organizations, or CROs, to conduct our ongoing and planned clinical trials. We also expect to engage CROs for any of our other product candidates that may progress to clinical development. We expect to rely on CROs, as well as other third parties, such as clinical data management organizations, medical institutions and clinical investigators, to conduct those clinical trials. Agreements with such third parties might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, our product development activities would be delayed.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with regulatory standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Similar regulatory requirements apply outside the United States, including the International Council for Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, or ICH.

We are also required to register certain ongoing clinical trials and post the results of certain completed clinical trials on government-sponsored, publicly accessible databases, such as, ClinicalTrials.gov, within specified timeframes. Failure to do so by us or third parties can result in FDA refusal to approve applications based on the clinical data, enforcement actions, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. 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 will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our product candidates.

In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and may receive cash or equity compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, or the FDA concludes that the financial relationship may have affected the results of the trial, the integrity of the data generated at the applicable clinical trial site may be questioned and the utility of the clinical trial itself may be jeopardized, which could result in the delay or

rejection by the FDA of any NDA we submit. Any such delay or rejection could prevent us from commercializing our product candidates.

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

We rely on collaborations with third parties for the development of our product candidates, and we may seek additional collaborations in the future. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

We have limited capabilities for drug development and do not yet have any capabilities for sales, marketing or distribution. Additionally, our product development programs and the commercialization of our product candidates will require substantial additional cash to fund expenses. As a result of these factors, we are, and expect to continue to be, dependent on collaborations relating to the development and commercialization of our existing and future product candidates. We currently have a collaborative relationship with Zai Lab to develop durlobactam and SUL-DUR in the Asia-Pacific region and with GARDP to develop zoliflodacin in a Phase 3 registration trial in uncomplicated gonorrhea. We have had and will continue to have discussions on potential partnering opportunities with various pharmaceutical companies. In addition, we may seek third-party collaborators for the development and commercialization of our product candidates, particularly for the commercialization of our product candidates either within or outside the United States. Our likely collaborators for any collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies and we may face significant competition in seeking appropriate collaborators. If we fail to enter into or maintain collaborations on reasonable terms or at all, our ability to develop our existing or future product candidates could be delayed, the commercial potential of our products could change, and our costs of development and commercialization could increase. If we enter into any future collaboration arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Our collaborations with Zai Lab, NIAID and GARDP and any future collaborations we might enter into may pose a number of risks, including:

- collaborators often have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected or contractually obligated;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval 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 of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such 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 or defend our or their intellectual property rights or may use our or their proprietary information in such a way as to invite litigation that could jeopardize or invalidate such intellectual property or proprietary information or expose us to potential litigation;

- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability;

- collaborators may be subject to geo-political actions, natural disasters or other occurrences, including public health epidemics such as the COVID-19 pandemic currently impacting China and elsewhere;

- collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates; and

- collaborators' decisions may limit the availability of the product supplies required for development, clinical and commercial activities.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our drug development or commercialization program could be delayed, diminished or terminated.

The failure of Zai Lab or GARDP to adequately perform their obligations and responsibilities in connection with the regulatory submissions for the approval of SUL-DUR or the conduct of the Phase 3 registration trial of zoliflodacin, respectively, could harm our business because we may not obtain regulatory approval for SUL-DUR or zoliflodacin in a timely manner, or at all.

We have entered into a license and collaboration agreement with Zai Lab, pursuant to which they managed the portion of our Phase 3 registration trial of SUL-DUR for *Acinetobacter* infections conducted in China and are responsible for all interactions with regulatory authorities within their territory, including China. We have also entered into an arrangement with GARDP pursuant to which it is conducting the Phase 3 registration trial of zoliflodacin in patients with uncomplicated gonorrhea. Under our arrangement with Zai Lab, Zai Lab funded most of our clinical trial costs in China for SUL-DUR, including all costs for our Phase 3 registration trial for *Acinetobacter* infections. Under our agreement with GARDP, GARDP will fund all the Phase 3 development costs for zoliflodacin, including costs of the manufacture and supply of the product candidate, and will take the lead in Phase 3 clinical development activities. While we continue to provide operational and logistical support for the Phase 3 registration trials, we have limited control of the activities of our collaborators. We cannot control whether our collaborators will devote sufficient time and resources to the Phase 3 registration trials or subsequent regulatory interactions, or if they will comply with applicable regulations and other requirements in jurisdictions where they operate. If either Zai Lab or GARDP does not successfully carry out its obligations and responsibilities or meet expected deadlines, or if the quality or accuracy of the clinical data either obtains is compromised due to the failure to adhere to clinical protocols, regulatory requirements or for other reasons, the Phase 3 registration trial of zoliflodacin may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize, either SUL-DUR or zoliflodacin. As a result, our results of

operations and the commercial prospects for SUL-DUR or zoliflodacin would be harmed, our costs could increase and our ability to generate revenues could be delayed.

Although Zai Lab and GARDP are each responsible for conducting specified Phase 3 registration trial activities, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on our collaborators does not relieve us of our regulatory responsibilities. We are required to comply with GCP for any product candidate of ours in clinical development. Regulatory authorities enforce GCP through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we fail to comply with applicable GCP, the clinical data generated in our trials may be deemed unreliable and the FDA or foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP requirements. In addition, we must conduct our clinical trials with drug product manufactured under current good manufacturing practices, or cGMP, requirements. Failure to comply with any of these regulations may require us to repeat preclinical studies and clinical trials, which would delay the regulatory approval process.

Our reliance on third parties to manufacture our product candidates increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not own or operate manufacturing facilities to produce clinical or commercial supplies of the product candidates that we are developing or evaluating. We have limited personnel with experience in drug manufacturing and lack the resources and the capabilities to manufacture any of our product candidates on a clinical or commercial scale. We currently rely on third parties for supply of our product candidates, and our strategy is to outsource all manufacturing of our product candidates and approved products, if any, to third parties.

To conduct clinical trials of our product candidates, we will need to identify suitable manufacturers with the capabilities to manufacture our compounds in large quantities in a manner consistent with existing regulations. Our third-party manufacturers may be unable to successfully increase the manufacturing capacity for any of our product candidates in a timely or cost-effective manner, or at all. In addition, quality issues may arise during scale-up activities and at any other time. If our manufacturers are unable to successfully scale up the manufacture of our product candidates in sufficient quality and quantity, the development, testing and clinical trials of that product candidate may be delayed, or infeasible, and regulatory approval or commercial launch of that product candidate may be delayed or not obtained, which could significantly harm our business.

In addition, we plan to develop certain product candidates for use as a fixed-dose combination therapy. If manufacturing or other issues result in a supply shortage of sulbactam, cefpodoxime or any other currently approved drug that we may study in combination with durlobactam, ETX0282 or any of our future product candidates, we may not be able to complete clinical development of our product candidates on our current timeline or at all.

We do not currently have any agreements with third-party manufacturers for the long-term commercial supply of any of our product candidates. In the future, we may be unable to enter into agreements with third-party manufacturers for commercial supplies of our product candidates or may be unable to do so on acceptable terms.

Even if we can establish and maintain arrangements with third-party manufacturers, reliance on third-party manufacturers entails risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how;

- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us; and

- supply chain disruptions due to geo-political actions, natural disasters or public healthy crises, including epidemics such as the COVID-19 pandemic.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us. Furthermore, we intend to develop certain product candidates as a fixed-dose combination with β-lactams and only a limited number of cGMP manufacturers are capable of handling β-lactam antibiotics.

If the third parties that we engage to supply any materials or manufacture product for our preclinical tests and clinical trials should cease to continue to do so for any reason, we likely would experience delays in advancing these trials while we identify and qualify replacement suppliers, and we may be unable to obtain replacement supplies on terms that are favorable to us. In addition, if we are not able to obtain adequate supplies of our product candidates or the substances used to manufacture them or any of the approved drugs we use in our combination trials, it will be more difficult for us to develop our product candidates and compete effectively.

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

We may not be able to win government or non-profit contracts or grants to fund our product development activities.

Historically, we have relied in part on funding from contracts or grants from government agencies and non-profit entities and it is part of our strategy to continue to do so. Such contracts or grants can be highly attractive because they provide capital to fund the on-going development of our product candidates without diluting our stockholders. However, there is often significant competition for these contracts or grants. Entities offering contracts or grants may have requirements to apply for or to otherwise be eligible to receive certain contracts or grants that our competitors may be able to satisfy that we cannot. In addition, such entities may make arbitrary decisions as to whether to offer contracts or make grants, to whom the contracts or grants will be awarded and the size of the contracts or grants to each awardee. Even if we can satisfy the award requirements, there is no guarantee that we will be selected to receive any contract or grant. If we are not successful in achieving this form of funding for our clinical trials, we will need to seek alternative means of funding which may not be available to the same extent, if at all.

Our reliance on government funding for certain of our programs adds uncertainty to our research, development and commercialization efforts with respect to those programs and may impose requirements that increase the costs of the research, development and commercialization of product candidates developed under those government-funded programs.

Aspects of our development programs are currently being supported, in part, with funding from the NIH, NIAID, CARB-X and the DOD. Contracts and grants awarded by the U.S. government, its agencies and its partners, including our awards from the NIH, NIAID, CARB-X, and the DOD, include provisions that reflect the government’s

substantial rights and remedies, many of which are not typically found in commercial contracts, including powers of the government to:

- terminate agreements, in whole or in part, for any reason or no reason at all;
- provide grant support to potential competitor programs;
- reduce or modify the government's obligations under such agreements without the consent of the other party;
- claim rights, including intellectual property rights, in products and data developed under such agreements;
- audit contract-related costs and fees, including allocated indirect costs;
- suspend the contractor or grantee from receiving new contracts pending resolution of alleged violations of procurement laws or regulations;
- impose U.S. manufacturing requirements for products that embody inventions conceived or first reduced to practice under such agreements;
- suspend or debar the contractor or grantee from doing future business with the government;
- control and potentially prohibit the export of products;
- pursue criminal or civil remedies under the False Claims Act, False Statements Act and similar remedy provisions specific to government agreements; and
- limit the government's financial liability to amounts appropriated by the U.S. Congress on a fiscal-year basis, thereby leaving some uncertainty about the future availability of funding for a program even after it has been funded for an initial period.

We may not have the right to prohibit the U.S. government from using certain technologies developed by us, and we may not be able to prohibit third-party companies, including our competitors, from using those technologies in providing products and services to the U.S. government. The U.S. government generally takes the position that it has the right to royalty-free use of technologies that are developed under U.S. government contracts.

In addition, government contracts and grants, and subcontracts and subawards awarded in the performance of those contracts and grants, normally contain additional requirements that may increase our costs of doing business, reduce our profits, and expose us to liability for failure to comply with these terms and conditions. These requirements include, for example:

- specialized accounting systems unique to government awards;
- mandatory financial audits and potential liability for price adjustments or recoupment of government funds after such funds have been spent;
- adhering to stewardship principals imposed by CARB-X as a condition of the award;
- public disclosures of certain award information, which may enable competitors to gain insights into our research program; and

- mandatory socioeconomic compliance requirements, including labor standards, non-discrimination and affirmative action programs and environmental compliance requirements.

As an organization, we are relatively new to government contracting and new to the regulatory compliance obligations that such contracting entails. If we fail to maintain compliance with those obligations, we may be subject to potential liability and termination of our contracts.

As a U.S. government contractor, we are subject to financial audits and other reviews by the U.S. government of our costs and performance on their contracts, as well as our accounting and general business practices related to these contracts. Based on the results of its audits, the government may adjust our contract-related costs and fees, including allocated indirect costs.

Risks Related to the Commercialization of Our Product Candidates

If we are unable to establish sales, marketing, market access, manufacturing and distribution capabilities for our product candidates, or enter into sales, marketing and distribution agreements with third parties, we may not be successful in commercializing our product candidates, if and when they are approved.

We do not have a sales, marketing, or market access infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any product candidate for which we may obtain marketing approval, we will need to establish a sales, marketing and market access organization or enter into collaboration, distribution and other sales, marketing and/or market access arrangements with one or more third parties to commercialize our product candidates. In the United States, we are evaluating whether to build our own commercial organization to target sites of care with the greatest incidence of serious and life-threatening multidrug-resistant infections and recruit experienced sales, marketing, market access and distribution professionals, leverage the experience and capabilities of an established commercial organization, or engage a third party who will establish select commercial capabilities on our behalf. The development of sales, marketing, market access and distribution capabilities will require substantial resources, will be time-consuming and could delay any product launch. We are considering working with multi-national pharmaceutical companies or experienced regional healthcare companies to leverage their commercialization capabilities to commercialize any product candidate for which we may obtain regulatory approval either within and/or outside of the United States.

If the commercial launch of a product candidate for which we, or a third party, recruit a sales force and establish marketing, market access 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, marketing and market access 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 to target the sites of care that we intend to target. If we are unable to establish a sales force, marketing, market access and distribution capabilities, our operating results may be adversely affected.

Factors that may inhibit our or our collaborators efforts to commercialize our drugs include:

- inability to recruit, train and retain adequate numbers of effective sales, marketing and market access personnel;

- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;

- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage compared to companies with more extensive product lines;

- unforeseen costs and expenses associated with creating or contracting with a third party to create a sales, marketing and market access organization; and

- unforeseen costs and limitations regarding setting up a distribution network.

If we are unable to establish our own sales, marketing, market access and distribution capabilities in the United States and, instead, enter into arrangements with third parties to perform these services, our revenues from these products and our profitability, if any, could potentially be lower than if we were to sell, market and distribute any product candidates that we develop ourselves. We intend to work with multi-national pharmaceutical companies or experienced healthcare companies to assist with the commercialization outside the United States of any of our product candidates that receive regulatory approval. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are favorable to us. We likely will have limited control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our product candidates effectively. If we do not establish sales, marketing, market access and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

Even if any of our product candidates receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success.

Even if we obtain approvals from the FDA, the EMA or other comparable regulatory agencies and can initiate commercialization of a product candidate we develop, 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. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on several factors, including:

- the efficacy and potential advantages compared to alternative treatments;
- the potential and perceived advantages and disadvantages of the product candidates, including cost and clinical benefit relative to alternative treatments;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- acceptance by physicians, patients, operators of hospitals, including in-hospital formularies, 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 ability to manufacture our product in sufficient quantities and yields;
- the strength and effectiveness of marketing and distribution support;
- the prevalence and severity of any side effects;
- 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;
- the emergence of bacterial resistance to the product; and
- the rate at which resistance to other drugs in the target infections grow.

Any failure by any of our product candidates that obtains regulatory approval to achieve market acceptance or commercial success would have a material adverse effect on our business prospects.

We face substantial competition, which may result in others discovering, developing, or commercializing products before or more successfully than we do.

The development and commercialization of new drug products is highly competitive. We face competition from major multi-national pharmaceutical companies, biotechnology companies, specialty pharmaceutical companies and generic drug companies with respect to our current and future product candidates. There are several large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of product candidates for the treatment of 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, more effectively marketed and sold or less costly than our product candidates, which could render our product candidates non-competitive and obsolete.

We are initially developing SUL-DUR for the treatment of pneumonia and bloodstream infections caused by multidrug-resistant *Acinetobacter*. Due to rising resistance rates, standard-of-care treatment for multidrug-resistant *Acinetobacter* often includes a combination of several last-line treatment options, including carbapenems, tetracyclines and polymyxins, all generically available agents. As of the date of this report, we are not aware of any marketed antibiotic that is indicated for the treatment of multidrug-resistant *Acinetobacter* infections; however, we are aware of other potentially competitive products that have shown *in vitro* activity against some strains of *Acinetobacter.*

We are initially developing zoliflodacin for the treatment of uncomplicated gonorrhea due to *N. gonorrhoeae* infections, including multidrug-resistant strains. Gonorrhea is commonly treated with the combination therapy of intramuscular ceftriaxone injection and oral azithromycin, both generically available agents. Additional generic cephalosporins and fluoroquinolones are also prescribed, but not recommend as primary treatment options given current resistance rates. Gepotidacin, currently under development for a variety of infections by GlaxoSmithKline plc, is the only potentially competitive product candidate in late-phase clinical development that we are aware of that is addressing gonorrhea.

We have initially developed ETX0282CPDP for the treatment of cUTIs, including those caused by multidrug-resistant *Enterobacteriaceae*. There are a variety of generically available antibiotic classes available for the treatment of such infections, including cephalosporins, carbapenems and fluoroquinolones. Additionally, there are several IV approved branded agents targeting multidrug-resistant cUTIs. We are aware of additional potentially competitive oral product candidates that may address a limited breadth of multidrug-resistant Gram-negative pathogens.

If our competitors obtain marketing approval from the FDA, the EMA or other comparable regulatory authorities for their product candidates more rapidly than we do, it could result in our competitors establishing a strong market position before we are able to enter the market.

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 as an organization. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any product candidates that we may develop. Our competitors also may obtain approval from the FDA, the EMA or other comparable regulatory agencies for their product candidates more rapidly than we may obtain approval for ours, which could result in product approval delays if a competitor obtains market exclusivity from the FDA or the EMA, or our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic drugs. Additional drugs may become available on a generic basis over the coming years. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic drugs.

Coverage and adequate reimbursement may not be available for our current or any future product candidates, which could make it difficult for us to sell profitably, if approved.

Market acceptance and sales of any product candidates that we or our collaborators commercialize will depend in part on the extent to which reimbursement for these drugs and related treatments will be available from third-party payors, including government health care programs (such as Medicare and Medicaid), government health administration authorities, managed care organizations and other private health insurers. Third-party payors decide which therapies they will pay for and establish reimbursement levels. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own coverage and reimbursement policies. However, decisions regarding the extent of coverage and amount of reimbursement to be provided for any product candidates that we develop will be made on a payor-by-payor basis. One payor's determination to provide coverage for a drug does not assure that other payors will also provide coverage and adequate reimbursement for the drug. Additionally, a third-party payor's decision to provide coverage for a therapy does not imply that an adequate reimbursement rate will be approved. Each payor determines whether it will provide coverage for a therapy, what amount it will pay the manufacturer for the therapy, and on what tier of its list of covered drugs, or formulary, it will be placed. The position on a payor's formulary, generally determines the co-payment that a patient will need to make to obtain the therapy and can strongly influence the adoption of such therapy by patients and physicians. Patients who are prescribed treatments for their conditions and providers prescribing such services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use our drugs, and providers are unlikely to prescribe our drugs, unless coverage is provided, and reimbursement is adequate to cover a significant portion of the cost of our drugs and their administration.

A primary trend in the United States healthcare industry and elsewhere is cost containment. Third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. We cannot be sure that coverage and reimbursement will be available for any drug that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Inadequate coverage and reimbursement may impact the demand for, or the price of, any drug for which we obtain marketing approval. If coverage and adequate reimbursement are not available, or are available only to limited levels, we may not be able to successfully commercialize our current and any future product candidates that we develop.

Product liability lawsuits against us could cause us to incur substantial liabilities and to limit commercialization of any products that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercially sell any drugs that we may develop. If we cannot successfully defend ourselves against claims that our product candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- reduced resources of our management to pursue our business strategy;
- decreased demand for any product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;

- initiation of investigations by regulators;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- significant costs to defend the resulting litigation;
- substantial monetary awards paid to clinical trial participants or patients;
- loss of revenue; and
- the inability to commercialize any drugs that we may develop.

We currently hold $10.0 million in product liability insurance coverage in the aggregate, with a per incident limit of $10.0 million, which may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

There are a variety of risks associated with marketing our product candidates internationally, which could affect our business.

We or our collaborators may seek regulatory approval for our product candidates outside of the United States and, accordingly, we expect that we will be subject to additional risks related to operating in foreign countries if we obtain the necessary approvals, including:

- differing regulatory requirements in foreign countries;
- the potential for so-called parallel importing, which is what happens when a local seller, faced with high or higher local prices, opts to import goods from a foreign market with low or lower prices rather than buying them locally;
- unexpected changes in tariffs, trade barriers, price and exchange controls and other regulatory requirements;
- economic weakness, including inflation, or political instability in foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- reduced level of reimbursement, pricing and insurance regimes compared to the United States;
- potential liability under the Foreign Corrupt Practices Act of 1977 or comparable foreign regulations;

- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;

- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and

- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods, fires, and public health epidemics, such as the COVID-19 pandemic currently impacting China and elsewhere.

These and other risks associated with our international operations may compromise our ability to achieve or maintain profitability.

Risks Related to Our Business and Managing Our Growth

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

We are highly dependent on the management, research and development, clinical, financial and business development expertise of Manoussos Perros, Ph.D., our chief executive officer, David Altarac, M.D., our chief medical officer, John Mueller, Ph.D., our chief development officer, Ruben Tommasi, Ph.D., our chief scientific officer, Matt Ronsheim, Ph.D., our chief pharmaceutical sciences and manufacturing officer, and Anna Diaz Triola, our chief commercial officer, as well as the other members of our scientific and clinical teams. Although we have employment agreements with our executive officers, each of them may nevertheless terminate their employment with us at any time. We do not maintain “key person” insurance for any of our executives or employees.

Recruiting and retaining qualified scientific and clinical personnel and, if we progress the development of any of our product candidates, commercialization, manufacturing and sales and marketing personnel, will be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. 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 successfully develop, gain regulatory approval of and commercialize our product candidates. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these 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 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 pursue our growth strategy will be limited.

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

As of December 31, 2021, we had 51 full-time employees. As the clinical development of our product candidates progresses, we also expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of quality and regulatory and medical affairs and, if any of our product candidates receives marketing approval, sales, marketing, product supply chain as well as G&A functions including IT and finance. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, potentially 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. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Risks Related to Our Intellectual Property

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

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our product candidates. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our technology and product candidates. If we do not adequately protect our intellectual property, competitors may be able to use our technologies and erode or negate any competitive advantage that we may have, which could harm our business and ability to achieve profitability. To protect our proprietary positions, we file patent applications in the United States and abroad related to our novel technologies and product candidates that are important to our business.

The patent application and prosecution process are expensive and time-consuming. We and our current licensees, or any future licensors and licensees may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. We or our current licensees, or any future licensors or licensees may also fail to identify patentable aspects of our research and development before it is too late to obtain patent protection.

Therefore, these and any of our patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, such as with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If our current licensees, or any future licensors or licensees, are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised, and we might not be able to prevent third parties from making, using and selling competing products. If there are material defects in the form or preparation of our patents or patent applications, such patents or applications may be invalid and/or unenforceable. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how. Any of these outcomes could impair our ability to prevent competition from third parties.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. For example, European patent law currently restricts the patentability of methods of treatment of the human body more than United States law does. In addition, the determination of patent rights with respect to pharmaceutical compounds and technologies commonly involves complex legal and factual questions, which has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Furthermore, recent changes in patent laws in the United States, including the America Invents Act of 2011, may affect the scope, strength and enforceability of our patent rights or the nature of proceedings that may be brought by us related to our patent rights.

We may not be aware of all third-party intellectual property rights potentially relating to our current and future our product candidates. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Similarly,

should we own any patents or patent applications in the future, we may not be certain that we were the first to file for patent protection for the inventions claimed in such patents or patent applications. As a result, the issuance, scope, validity and commercial value of our patent rights cannot be predicted with any certainty. Moreover, we may be subject to a third-party pre-issuance submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or become involved in derivation, ex-parte reexamination, or *inter partes* review proceedings in the USPTO or similar proceedings elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. If the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Our pending and future patent applications may not result in patents being issued that protect our technology or product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection against competing products or processes sufficient to achieve our business objectives, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may seek to market generic versions of any approved products by submitting abbreviated new drug applications to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable and/or not infringed. Alternatively, our competitors may seek approval to market their own products similar to or otherwise competitive with our products. In these circumstances, we may need to defend and/or assert our patents, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid and/or unenforceable.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate, a patent being held unenforceable, and/or in one or more or in patent claims being narrowed or invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products or limit the duration of the patent protection of our technology and products.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

Patents have a limited lifespan. In the U.S., if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest filing date of a non-provisional application to which the patent claims priority. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product candidate, we may be open to competition from competitive medications, including generic medications. 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 owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing product candidates similar or identical to ours.

In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Depending upon the timing, duration and conditions of any FDA marketing approval of our product candidates, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments, and similar legislation in the European Union, as discussed above. As a result, our revenue from applicable products could be reduced. Further, 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, and our competitive position, business, financial condition, results of operations, and prospects could be materially harmed.

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 and other third parties may infringe our issued patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, trademarks, copyrights or other intellectual property. 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 or that one or more claims of a patent are invalid, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. 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 basis 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. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

In any infringement litigation, any award of monetary damages we receive may not be commercially valuable. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. 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. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. 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 because of the proceedings. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing, misappropriating or successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a negative impact on our ability to compete in the marketplace.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could significantly harm our business.

Our business success depends, in part, on our ability to discover, develop, manufacture, market and sell our product candidates without infringing the intellectual property and other proprietary rights of third parties. Numerous third-party U.S. and non-U.S. issued patents exist in the area of antibacterial treatment, including compounds, formulations, treatment methods and synthetic processes that may be applied towards the synthesis of antibiotics. If any of their patents cover our product candidates or technologies, we may not be free to manufacture or market our product candidates as planned.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our technology or product candidates, including interference proceedings before the USPTO. Intellectual property disputes arise in several areas including with respect to patents, use of other proprietary rights and the contractual terms of license arrangements. Third parties may assert claims against us based on existing or future intellectual property rights. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance.

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

We may need to license intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property rights, including patent rights, that are important or necessary to the development of our product candidates. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our product candidates, in which case we would be required to obtain a license from these third parties. Such a license may not be available on commercially reasonable terms, or at all, and we could be forced to accept unfavorable contractual terms. If we are unable to obtain such licenses on commercially reasonable terms, our business could be harmed.

If we are unable to obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them 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 the affected technology and product candidates, which could materially harm our business, financial condition, results of operations, and prospects.

We may be subject to claims by third parties asserting that we or our employees, consultants or contractors have wrongfully used or disclosed confidential information of third parties, or we have wrongfully used or disclosed alleged trade secrets of their current or former employers, or claims asserting we have misappropriated their intellectual property 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. Although we try to ensure that our employees do not use the proprietary information or know-how of third parties in their work for us, we may be subject to claims that these employees or we have inadvertently or otherwise used intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. We may also in the future be subject to claims that we have caused an employee to breach the terms of his or her non-competition or non-solicitation agreement. Litigation may be necessary to defend against these potential claims.

In addition, while it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, such employees and contractors may breach the agreement and claim the developed intellectual property as their own.

Our business was founded in 2015 as a spin-out from AstraZeneca AB, or AstraZeneca. Although all patent applications are fully owned by us and were either filed by AstraZeneca with all rights fully transferred to us, or filed in our sole name, because we acquired certain of our patents from AstraZeneca, we must rely on their prior practices, regarding the assignment of such intellectual property. Our and their assignment agreements may not be self-executing or may be breached, and 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. A court could prohibit us from using technologies or features that are essential to our products if such technologies or features are found to incorporate or be derived from the trade secrets or

other proprietary information of the former employers. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and could be a distraction to management. In addition, any litigation or threat thereof may adversely affect our ability to hire employees or contract with independent service providers. Moreover, a loss of key personnel or their work product could hamper or prevent our ability to commercialize our products.

Any trademarks we may obtain may be infringed or successfully challenged, resulting in harm to our business.

We expect to rely on trademarks as one means to distinguish any of our product candidates that are approved for marketing from the products of our competitors. Once we select trademarks and apply to register them, our trademark applications may not be approved. Third parties may oppose our trademark applications, or otherwise challenge our use of the trademarks. If our trademarks are successfully challenged, we could be forced to rebrand our products, which could result in loss of brand recognition and could require us to devote resources to advertising and marketing new brands. Our competitors may infringe our trademarks and we may not have adequate resources to enforce our trademarks.

In addition, any proprietary name we propose to use with a 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 the 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 to identify a suitable proprietary product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patent and trademark protection for our product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect our trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties prior to beginning research or disclosing proprietary information. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets. Despite these efforts and the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information due to our reliance on third parties, increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements.

Monitoring unauthorized uses and disclosures of our intellectual property is difficult, and we do not know whether the steps we have taken to protect our intellectual property will be effective. In addition, we may not be able to obtain adequate remedies for any 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 inside and outside the United States are less willing or unwilling to protect trade secrets.

Moreover, our competitors may independently develop knowledge, methods and know-how equivalent to our trade secrets. Competitors could purchase our products and replicate some or all the competitive advantages we derive from our development efforts for technologies on which we do not have patent protection. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, 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 competitive position would be harmed.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. In some cases, we may not be able to obtain patent protection for certain licensed technology outside the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States, even in jurisdictions where we do pursue patent protection. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, even in jurisdictions where we do pursue patent protection or from selling or importing products made using our inventions in and into the United States or other jurisdictions. 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 pursued and obtained patent protection to develop their own products and, further, may export otherwise 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 preclinical programs 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, if pursued and obtained, or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our 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.

Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters

Even if we complete the necessary preclinical studies and clinical trials, the regulatory approval process is expensive, time-consuming and uncertain and may prevent us or any future collaborators from obtaining approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we, or any future collaborators, will obtain marketing approval to commercialize a product candidate.

Our product candidates and the activities associated with their development and commercialization, including their design, research, testing, manufacture, safety, efficacy, quality control, recordkeeping, labeling, packaging, storage, approval, advertising, promotion, sale, distribution, import, export, and reporting of safety and other post-market information, are subject to comprehensive regulation by the FDA, the EMA and other foreign regulatory agencies. Failure to obtain marketing approval for a product candidate will prevent us or a potential collaborator from commercializing the product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and will rely on third parties to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. We may not be able to successfully manufacture our products in compliance with applicable requirements such as GMPs. If any of our product candidates

receives marketing approval, the accompanying label may limit its approved use more narrowly than we anticipate, which could limit sales of the product.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive and may take many years, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. The FDA, the EMA or other regulatory authorities may determine that our product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

In addition, changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable. Any marketing approval we, or any future collaborators, ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be impaired.

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

To market and sell our products in the European Union, or EU, and any other jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain approval from the FDA. The regulatory approval process outside the United States generally includes all the risks associated with obtaining approval from the FDA. 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, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, denial of approval in one jurisdiction may impact our ability to obtain approval elsewhere. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Even if we obtain marketing approvals for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we or our collaborators manufacture and market our products and compliance with such requirements may involve substantial resources, which could materially impair our ability to generate revenue.

Even if marketing approval of a product candidate is granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation, including the potential requirements to implement a REMS or to conduct costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. We must also comply with requirements concerning advertising and promotion for any of our product

candidates for which we obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved. In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements including ensuring that quality control and manufacturing procedures conform to cGMP, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements, among other things. We and our contract manufacturers could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMP. We must also comply with FDA requirements for adverse event reporting for commercial products.

Accordingly, assuming we receive marketing approval for one or more of our product candidates, we and our contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we are not able to comply with post-approval regulatory requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. We could also be subject to other civil or criminal penalties. Thus, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Any product candidate for which we obtain marketing approval could be subject to post-marketing restrictions or recall 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 any of them are approved.

The FDA and other federal and state agencies, including the U.S. DOJ, closely regulate compliance with all requirements governing prescription drug products, including requirements pertaining to marketing and promotion of drugs in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off-label use and if we market our products for indications other than their approved indications, we may be subject to enforcement action for off-label marketing. Violations of such requirements may lead to investigations alleging violations of the Food, Drug and Cosmetic Act and other statutes, including the False Claims Act and other federal and state health care fraud and abuse laws as well as state consumer protection laws.

Our failure to comply with all regulatory requirements, and later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, may yield various results, including:

- litigation involving patients taking our products;
- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;

- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Non-compliance by us or any future collaborator with regulatory requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with regulatory requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Non-compliance with U.K. and EU requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, also can result in significant financial penalties. Similarly, failure to comply with the U.K.'s or EU's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

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

We are exposed to the risk of employee fraud or other misconduct or failure to comply with applicable regulatory requirements. Misconduct by employees and independent contractors, such as principal investigators, CROs, consultants, commercial partners and vendors, could include failures to comply with regulations of the FDA, the EMA and other comparable regulatory authorities, to provide accurate information to such regulators, to comply with manufacturing standards we have established, to comply with healthcare fraud and abuse laws, to report financial information or data accurately or to disclose unauthorized activities to us. Sales, marketing and other business arrangements in the healthcare industry are subject to extensive laws intended to prevent fraud, kickbacks, self-dealing and other abusive practices. Employee and independent contractor misconduct could also involve the improper use of individually identifiable information, including, without limitation, information obtained during clinical trials, which could result in regulatory sanctions and serious harm to our reputation. In addition, federal procurement laws impose substantial penalties for misconduct in connection with government contracts and require certain contractors to maintain a code of business ethics and conduct. It is not always possible to identify and deter employee and independent contractor misconduct, and any precautions we take to detect and prevent improper activities 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. If any such actions are instituted against us, 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, contractual damages, reputational harm, diminished profits and future earnings, additional reporting or oversight obligations if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with the law and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate.

Our current and future relationships with healthcare professionals, principal investigators, consultants, customers and third-party payors in the United States and elsewhere may be subject, directly or indirectly, to applicable anti-kickback, fraud and abuse, false claims, physician payment transparency, health information privacy and security and other healthcare laws and regulations, which could expose us to penalties.

Our current and future arrangements with healthcare professionals, principal investigators, consultants, customers and third-party payors may expose us to broadly applicable fraud and abuse and other healthcare laws, including, without limitation, the federal Anti-Kickback Statute and the federal False Claims Act, that may constrain the business or financial arrangements and relationships through which we research, sell, market and distribute any product candidates for which we obtain marketing approval. In addition, we may be subject to physician payment transparency laws and patient privacy and security regulation by the federal government and by the states and foreign jurisdictions in which we conduct our business. The applicable federal, state and foreign healthcare laws that may affect our ability to operate include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under federal healthcare programs such as Medicare and Medicaid;

- federal civil and criminal false claims laws, including the federal False Claims Act, which impose criminal and civil penalties, including through civil whistleblower or *qui tam* actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

- the civil monetary penalties statute, which imposes penalties against any person or entity who, among other things, is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent;

- HIPAA, which created additional federal criminal and civil statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of whether the payor is public or private, knowingly and willfully embezzling or stealing from a health care benefit program, willfully obstructing a criminal investigation of a health care offense and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;

- HIPAA, as amended by the HITECH Act of 2009, and their respective implementing regulations, which impose obligations on "covered entities," including certain healthcare providers, health plans, and healthcare clearinghouses, as well as their respective "business associates" that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal Physician Payments Sunshine Act, created under Section 6002 of Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the ACA, and its implementing regulations, which created annual reporting requirements for manufacturers of drugs, devices, biologicals and medical supplies for certain payments and "transfers of value" provided to covered recipients, including physicians, as defined by such law, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

- analogous state and foreign laws, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers; state 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 or to adopt compliance programs as prescribed by state laws and regulations, or that otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures and drug pricing; state and local laws requiring the licensure of pharmaceutical sales representatives; and 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 often are not preempted by HIPAA, thus complicating compliance efforts.

Further, the ACA, among other things, amended the intent requirement of the federal Anti-Kickback Statute and certain criminal statutes governing healthcare fraud. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. In addition, the ACA provided that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

Efforts to ensure that our future business arrangements with third parties will comply with applicable healthcare laws and regulations may involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, including, without limitation, damages, monetary fines, disgorgement, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional reporting or oversight obligations if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with the law and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and pursue our strategy. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including future collaborators, are found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government healthcare programs, which could also affect our business.

Future legislation, and/or regulations and policies adopted by the FDA, the EMA or comparable regulatory authorities, may increase the time and cost required for us or our collaborators to conduct and complete clinical trials of our current and future product candidates.

The FDA and the EMA have each established regulations to govern the product development and approval process, as have other foreign regulatory authorities. The policies of the FDA, the EMA and other regulatory authorities may change. For example, in December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation, but not all its provisions have yet been implemented. Additionally, in August 2017, the FDA issued final guidance setting forth its current thinking with respect to development programs and clinical trial designs for antibacterial drugs to treat serious bacterial diseases in patients with an unmet medical need. We cannot predict what if any effect the Cures Act or any existing or future guidance from the FDA or other regulatory authorities will have on the development of our product candidates.

Recently enacted and future legislation may increase the difficulty and cost for us and our collaborators to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval.

Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access.

Other federal health reform measures have been proposed and adopted in the United States. For example, the Medicare Access and CHIP Reauthorization Act of 2015 ended the use of the statutory formula for clinician payment and established a quality payment incentive program, also referred to as the Quality Payment Program. This program provides clinicians with two ways to participate, including through the Advanced Alternative Payment Models, or APMs, and the Merit-based Incentive Payment System, or MIPS. In November 2019, CMS issued a final rule finalizing the changes to the Quality Payment Program. It is unclear how payment reductions or the introduction of the Quality Payment Program will impact overall physician reimbursement under the Medicare program. It is also unclear if changes in Medicare payments to providers would impact such providers' willingness to prescribe and administer our products, if approved.

Further, there has been heightened governmental scrutiny over the way companies set prices for their marketed products. For example, there have been 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 patient programs, and reform government program reimbursement methodologies for drug products.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us or our collaborators from being able to generate revenue, attain profitability, or commercialize our drugs.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

Our product candidates may be subject to government price controls that may affect our revenue.

There has been heightened governmental scrutiny in the United States and abroad of pharmaceutical pricing practices considering the rising cost of prescription drugs and biologics. In the United States, such scrutiny has resulted in several recent Congressional inquiries and proposed and enacted federal 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 former Trump Administration's budget proposal for fiscal year 2020 contained further drug price control measures that could be enacted during the 2020 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. The former Trump Administration also released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug 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 solicited feedback on some of these measures and has implemented others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that was effective January 1, 2019. On November 20, 2020, CMS issued an interim final rule through the CMS Innovation Center whereby Medicare Part B reimbursement for "certain high-cost prescriptions drugs" would be no more than most-favored-nation price (i.e.,

the lowest price) after adjustments, for a pharmaceutical product that the drug manufacturer sells in a member country of the Organization for Economic Cooperation and Development that has a comparable per-capita gross domestic product. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. While some of these and other measures may require additional authorization to become effective, members of Congress have and the new Biden Administration have indicated that they will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have become 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.

Outside of the United States, particularly in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed.

We are subject to the U.K. Bribery Act, the U.S. Foreign Corrupt Practices Act and other anti-corruption laws, as well as export control laws, import and customs laws, trade and economic sanctions laws and other laws governing our operations.

Our operations are subject to anti-corruption laws, including the U.K. Bribery Act 2010, or the Bribery Act, the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. §201, the U.S. Travel Act, and other anti-corruption laws that apply in countries where we do business. The Bribery Act, the FCPA and these other laws generally prohibit us and our employees and intermediaries from authorizing, promising, offering, or providing, directly or indirectly, improper or prohibited payments, or anything else of value, to government officials or other persons to obtain or retain business or gain some other business advantage.

Under the Bribery Act, we may also be liable for failing to prevent a person associated with us from committing a bribery offense. We, our collaborators, and those acting on our behalf operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we participate in collaborations and relationships with third parties whose corrupt or illegal activities could potentially subject us to liability under the Bribery Act, FCPA or local anticorruption laws, even if we do not explicitly authorize or have actual knowledge of such activities. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject, or the way existing laws might be administered or interpreted.

Compliance with the Bribery Act, the FCPA and these other laws is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, anti-corruption laws present challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to enforcement actions.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United States and the United Kingdom, and authorities in the European Union, including applicable export control regulations, economic sanctions and embargoes on certain countries and persons, anti-money laundering laws, import and customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. Likewise,

any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United States, United Kingdom or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition. Further, the failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting.

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

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

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

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

Recent and potential future changes to U.S. and non-U.S. tax laws could materially adversely affect our company.

Existing, new or future changes in tax laws, regulations and treaties, or the interpretation thereof, in addition to tax policy initiatives and reforms under consideration in the United States or internationally and other initiatives could have an adverse effect on the taxation of international businesses. Furthermore, countries where we are subject to taxes, including the United States, are independently evaluating their tax policy and we may see significant changes in legislation and regulations concerning taxation. On December 22, 2017, President Trump signed into law the Tax Act, which significantly revised the Code. The Tax Act, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits.

Notwithstanding the reduction in the corporate income tax rate, the overall impact of the Tax Act is uncertain and our business and financial condition could be adversely affected. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. Other legislative changes could also affect the taxation of holders of our common stock. We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our effective tax rates in the future in countries where we have operations and have an adverse effect on our overall tax rate in the future, along with increasing the complexity, burden and cost of tax compliance. We urge our stockholders to consult with their legal and tax advisors with respect to any such legislative changes and the potential tax consequences of investing in or holding our common stock.

Risks Related to Ownership of Our Common Stock

Innoviva, Inc. may exert a substantial influence on actions requiring stockholder vote, potentially in a manner that you do not support.

As of December 31, 2021, Innoviva, held approximately 59.9% of our issued and outstanding shares of common stock, and accordingly controls 59.9% of our voting power. Innoviva's large ownership stake may allow it to exert a significant influence on actions requiring a stockholder vote, potentially including amendments to our certificate of incorporation, election of our board of directors, removal of any of our directors, adoption of measures that could delay or prevent a change in control or impede a merger, takeover, or other business combination involving us, and approval of other major corporate transactions. In addition, Innoviva's stock ownership may discourage a potential acquirer from making a tender offer or otherwise attempting to obtain control of us, which in turn could reduce our stock price or prevent our stockholders from realizing a premium over our stock price. Innoviva has appointed an Observer to our Board, and retains the right to appoint two directors to our Board so long as it maintains certain thresholds of stock ownership, which it presently exceeds. As a result of its stock ownership and ability to appoint directors to our Board, Innoviva has the ability to significantly influence management and to exercise control over our business. Stockholders other than Innoviva correspondingly do not have the ability to influence management or exercise control over the business.

The trading price of our common stock may be volatile and fluctuate substantially, and you could lose all or part of your investment.

Since our initial public offering, our stock price has been and is likely to continue to be highly volatile and could be subject to wide fluctuations in response to several factors, some of which are beyond our control, including limited trading volume. The stock market in general and the market for biopharmaceutical companies have experienced extreme volatility that has often been unrelated to the operating performance of companies. As a result of this volatility, investors may not be able to sell their shares at or above the price paid for the shares. In addition to the factors discussed in this "Risk Factors" section, these factors include:

- the commencement, enrollment or results of our planned and future clinical trials;
- the loss of any of our key scientific or management personnel;
- regulatory or legal developments in the United States and other countries;
- the success of competitive products or technologies;
- adverse actions taken by regulatory agencies with respect to our clinical trials or manufacturers;
- changes or developments in laws or regulations applicable to our product candidates and preclinical program;
- changes to our relationships with collaborators, manufacturers or suppliers;
- the results of our testing and clinical trials;
- unanticipated safety concerns;
- announcements concerning our competitors or the pharmaceutical industry in general;
- changes in the structure of healthcare payment systems;
- actual or anticipated fluctuations in our operating results;

- changes in our financial results, including our ability to continue as a going concern, or changes of recommendations by securities analysts;
- potential acquisitions;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates;
- the trading volume of our common stock on The Nasdaq Global Market;
- sales of our common stock by us, our executive officers and directors or our stockholders or the anticipation that such sales may occur in the future;
- general economic, political and market conditions and overall fluctuations in the financial markets in the United States or the United Kingdom;
- stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biopharmaceutical industry; and
- investors' general perception of us, our business and the antibiotic sector.

These and other market and industry factors may cause the market price and demand for our common stock to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from selling their shares of our common stock at or above the price paid for the shares and may otherwise negatively affect the liquidity of our common stock. In addition, the stock market in general, and biopharmaceutical companies, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies.

Some companies that have experienced volatility in the trading price of their shares have been the subject of securities class action litigation. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our business practices. Defending against litigation is costly and time-consuming and could divert our management's attention and our resources. Furthermore, during litigation, there could be negative public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a negative effect on the market price of our common stock.

The issuance of additional shares of stock, or actual or perceived sales by large holders, could depress the market price of our common stock.

Our certificate of incorporation authorizes us to issue up to 125,000,000 shares of common stock and up to 10,000,000 shares of preferred stock with such rights and preferences as may be determined by our board of directors. Subject to compliance with applicable rules and regulations, we may issue our shares of common stock or securities convertible into our common stock from time to time in connection with a financing, acquisition, investment, our equity incentive plans or otherwise. Any such issuance could result in substantial dilution to our existing stockholders and cause the trading price of our common stock to decline.

Our common stock is concentrated in several shareholders who hold large positions. For example, Innoviva, held 59.9% of our issued and outstanding common stock and AstraZeneca held 4.5% of our issued and outstanding common stock as of December 31, 2021. If holders of large numbers of our shares sell a substantial number of our shares of common stock in the public markets, or if there is the perception that such sales could occur, such sales could depress the market price of our shares of common stock and impair our ability to raise capital through the sale of additional equity securities. We cannot predict neither the number of shares that might be sold by our current or future

investors nor the effect that future sales of our shares of common stock would have on the market price of our shares of common stock.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions and matters submitted to stockholders for approval.

Our executive officers, directors and current beneficial owners of 5% or more of our common stock and their respective affiliates beneficially own, in the aggregate, greater than 50% of our outstanding common stock, based on the number of shares of our common stock outstanding as of December 31, 2021. As a result, these persons, acting together, would be able to control all matters requiring stockholder approval, including the election and removal of directors, any merger, consolidation or sale of all or substantially all our assets, or other significant corporate transactions. The interests of this group of stockholders may not coincide with our interests or the interests of other stockholders. In addition, these persons, acting together, may have the ability to control the management and affairs of our company. Accordingly, this concentration of ownership may harm the market price of our common stock by: delaying, deferring, or preventing a change in control; entrenching our management and/or the board of directors; impeding a merger, consolidation, takeover, or other business combination involving us; or by discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us.

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

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

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the way stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be affected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a stockholder rights plan, or so-called “poison pill,” that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 66$^{2}/_{3}$% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired more than 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

We are an "emerging growth company" and because of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be less attractive to investors.

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not emerging growth companies, including:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- not being required to hold a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We currently take advantage of some or all these reporting exemptions and we may continue to do so until we are no longer an emerging growth company, or EGC. We will remain an EGC until the earlier of (1) the last day of 2023, (2) the last day of the fiscal year in which we have total annual gross revenue of at least $1.07 billion, (3) the last day of the fiscal year in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (4) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

Under Section 107(b) of the JOBS Act, emerging growth companies 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 exemption from new or revised accounting standards and, therefore, we are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting.

Our internal control over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner, or if we are unable to maintain proper and effective internal controls, we may not be able to produce timely and accurate financial statements. If that were to happen, the market price of our common stock could decline, and we could be subject to sanctions or investigations by Nasdaq, the SEC, or other regulatory authorities.

We have broad discretion in the use of our cash and cash equivalents and may invest or spend them in ways with which you do not agree and in ways that may not increase the value of your investment.

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

Because we do not anticipate paying any cash dividends on our common stock in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment.

You should not rely on an investment in our common stock to provide dividend income. Pursuant to our Business Transfer and Subscription Agreement with AstraZeneca, we also agreed to pay AstraZeneca a one-time milestone payment of $5.0 million within three months of achieving a specified cumulative net sales milestone for durlobactam. This milestone payment will be automatically waived should our common stock trade on Nasdaq at or above a specified price at the time we achieve such specified cumulative net sales milestone for durlobactam, subject to adjustment for share splits, dividends and other similar events. We are also obligated to pay AstraZeneca a one-time milestone payment of $10.0 million within two years of achieving the first commercial sale of zoliflodacin. Following the achievement of either milestone, we are not permitted to pay dividends or make other distributions to any of our stockholders until the applicable milestone payment has been paid in full or otherwise waived. We have never declared or paid a dividend on our common stock to date, and we currently intend to retain our future earnings, if any, to fund the development and growth of our business. As a result, capital appreciation, if any, on our common stock will be your sole source of gains for the foreseeable future. Investors seeking cash dividends should not purchase our common stock.

We incur significantly increased costs because of operating as a company whose common stock is publicly traded in the United States, and our management is required to devote substantial time to new compliance initiatives.

As a public company in the United States, we incur significant legal, accounting and other expenses that we did not incur previously. These expenses will likely be even more significant after we no longer qualify as an EGC. The Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of Nasdaq and other applicable securities rules and regulations impose various requirements on public companies in the United States, including the establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our senior management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased and will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance, which in turn could make it more difficult for us to attract and retain qualified senior management personnel or members for our board of directors.

However, these rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404, we will be required to furnish a report by our senior management on our internal control over financial reporting. However, while we remain an EGC, 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

prepare for compliance with Section 404, 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 consolidated financial statements.

General Risk Factors

Significant disruptions of our information technology systems or data security incidents could result in significant financial, legal, regulatory, business, and reputational harm to us.

We are increasingly dependent on information technology systems and infrastructure, including mobile technologies, to operate our business. In the ordinary course of our business, we collect, store, process and transmit substantial amounts of sensitive information, including intellectual property, proprietary business information, personal information and other confidential information. It is critical that we do so in a secure manner to maintain the confidentiality, integrity and availability of such sensitive information. We have also outsourced elements of our operations, including elements of our information technology infrastructure, to third parties and, as a result, we manage several third-party vendors who may or could have access to our computer networks or our confidential information. In addition, many of those third parties in turn subcontract or outsource some of their responsibilities to other third parties. While all information technology operations are inherently vulnerable to inadvertent or intentional security breaches, incidents, attacks and exposures, the accessibility and distributed nature of our information technology systems, and the sensitive information stored on those systems, make such systems potentially vulnerable to unintentional or malicious, internal and external attacks on our technology environment. Potential vulnerabilities can be exploited from inadvertent or intentional actions of our employees, third-party vendors, business partners, or by malicious third parties. Attacks of this nature are increasing in their frequency, levels of persistence, sophistication and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives (including industrial espionage) and expertise, including organized criminal groups, “hacktivists,” nation states and others. In addition to the extraction of sensitive information, such attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. In addition, the prevalent use of mobile devices increases the risk of data security incidents.

Significant disruptions of our, our third-party vendors’ or business partners’ information technology systems or other similar data security incidents could adversely affect our business operations and result in the loss, misappropriation, and unauthorized access, use or disclosure of, or the prevention of access to, sensitive information, which could result in financial, legal, regulatory, business and reputational harm to us. In addition, information technology system disruptions, whether from attacks on our technology environment or from computer viruses, natural disasters, terrorism, war and telecommunication and electrical failures, could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data.

There is no way of knowing with certainty whether we have experienced any data security incidents that have not been discovered. While we have no reason to believe this to be the case, attackers have become very sophisticated in the way they conceal access to systems, and many companies that have been attacked are not aware that they have been attacked. Any event that leads to unauthorized access, use or disclosure of personal information, including personal information regarding our patients or employees, could disrupt our business, harm our reputation, compel us to comply with applicable federal and state breach notification laws and foreign law equivalents, subject us to time-consuming, distracting and expensive litigation, regulatory investigation and oversight, mandatory corrective action, require us to verify the correctness of database contents, or otherwise subject us to liability under laws, regulations and contractual

obligations, including those that protect the privacy and security of personal information. This could result in increased costs to us and result in significant legal and financial exposure and reputational harm. In addition, any failure or perceived failure by us or our vendors or business partners to comply with our privacy, confidentiality or data security-related legal or other obligations to third parties, or any further security incidents or other inappropriate access events that result in the unauthorized access, release or transfer of sensitive information, which could include personally identifiable information, may result in governmental investigations, enforcement actions, regulatory fines, litigation, or public statements against us by advocacy groups or others, and could cause third parties, including clinical sites, regulators or current and potential partners, to lose trust in us, or we could be subject to claims by third parties that we have breached our privacy- or confidentiality-related obligations. Moreover, data security incidents 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. While we have implemented security, measures intended to protect our information technology systems and infrastructure, there can be no assurance that such measures will successfully prevent service interruptions or security incidents.

If we engage in future acquisitions or strategic collaborations, this may increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities and subject us to other risks.

From time to time, we may evaluate various acquisitions and strategic collaborations, including licensing or acquiring complementary drugs, intellectual property rights, technologies or businesses, as deemed appropriate to carry out our business plan. Any potential acquisition or strategic collaboration may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent liabilities;
- assimilation of operations, intellectual property and drugs of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing drug programs and initiatives in pursuing such a strategic partnership, merger or acquisition;
- retention of key employees, the loss of key personnel and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing drugs or drug candidates and regulatory approvals; and
- our inability to generate revenue from acquired technology and/or drugs sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

Tax authorities may disagree with our positions and conclusions regarding certain tax positions, resulting in unanticipated costs, taxes, or non-realization of expected benefits.

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, the Internal Revenue Service or another tax authority could challenge our allocation of income by tax jurisdiction and the amounts paid between our affiliated companies pursuant to our intercompany arrangements and transfer pricing policies, including amounts paid with respect to our intellectual property development. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a "permanent establishment" under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. The foregoing are only selected examples of potential challenges, and other tax positions we have taken or may take in the future could become the subject of disputes with one or more tax authorities. A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, in which case, we expect that we might contest such assessment.

Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our principal offices occupy 20,062 square feet of leased office, research and development and laboratory facility space in Waltham, Massachusetts, pursuant to a lease agreement that expires in December 2022. In February 2022 the Company made the decision to exercise the renewal option within the AZ lease which will extend the lease term for an additional three years. We believe that our current facilities are suitable to meet our current needs.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings and we are not aware of any pending or threatened legal proceeding against us that we believe could have a material adverse effect on our business, operating results or financial condition.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

Our common stock is traded on The Nasdaq Global Market under the symbol "ETTX."

Holders of Record

As of February 25, 2022, we had approximately 10 holders of record of our common stock. Certain shares are held in "street" name and accordingly, the number of beneficial owners of such shares is not known or included in the foregoing number. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividend Policy

We have never declared or paid a dividend on our common stock, and we do not anticipate declaring or paying dividends on our common stock in the foreseeable future. We currently intend to retain our future earnings, if any, to fund the development and growth of our business.

Pursuant to our Business Transfer and Subscription Agreement with AstraZeneca, we agreed to make two specified milestone payments to AstraZeneca. Following the achievement of either milestone, we are not permitted to pay dividends or make other distributions to any of our stockholders until the applicable milestone payment has been paid in full or otherwise waived. See the section titled "Business— License and Collaboration Agreements."

Recent Sales of Unregistered Equity Securities

On June 11, 2020, we completed a private placement transaction, the First Private Placement, in which we sold to Innoviva a total of 14,000,000 shares of our common stock and issued warrants to purchase an additional 14,000,000 shares of our common stock, with an exercise price per share of $2.50. The First Private Placement was closed in two tranches for total aggregate gross proceeds of $35.0 million.

On September 1, 2020, we completed a private placement transaction pursuant to a securities purchase agreement with the purchasers named therein, or the Investors, in which we sold to the Investors a total of 8,183,878 shares of our common stock, issued warrants to purchase an additional 9,345,794 shares of our common stock, with an exercise price per share of $2.675, and issued pre-funded warrants to purchase an additional 1,161,916 shares of our common stock, with an exercise price per share of $0.001, collectively, the Second Private Placement. The Second Private Placement resulted in total aggregate gross proceeds of approximately $25.0 million.

On June 11, 2021, we completed a private placement transaction, the Third Private Placement, in which we sold to Innoviva a total of 10,000,000 shares of our common stock and issued warrants to purchase an additional 10,000,000 shares of our common stock, with an exercise price per share of $2.00. The Third Private Placement was closed in two tranches for total aggregate gross proceeds of $20.0 million.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. Reserved

Not applicable.

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

You should read the following information in conjunction with the consolidated financial information and the notes thereto appearing elsewhere in this Annual Report on Form 10-K. In addition, you should read the "Risk Factors" and "Special Note Regarding Forward-Looking Statements" in this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are an advanced, late clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of targeted antibacterial products that address high unmet medical needs to treat serious infections caused by multidrug-resistant pathogens.

Our lead product candidate, sulbactam-durlobactam, or SUL-DUR, is an intravenous, or IV, combination of sulbactam, an IV β-lactam antibiotic, and durlobactam, a novel broad-spectrum IV β-lactamase inhibitor, or BLI, that we are developing for the treatment of pneumonia and bloodstream infections caused by carbapenem-resistant *Acinetobacter baumannii*, or *Acinetobacter*. Based on current carbapenem resistance rates, we estimate there are in excess of 250,000 hospital-treated carbapenem-resistant *Acinetobacter* infections annually across the United States, Europe, the Middle East and China for which significant morbidity and mortality exists due to limited treatment options. We initiated ATTACK (***A****cinetobacter* **T**reatment **T**rial **A**gainst **C**olistin), our single Phase 3 registration trial in 2019, and announced positive top-line Phase 3 data in October 2021. Based on the success of ATTACK and the totality of the SUL-DUR preclinical and clinical data, we also announced our intention to file a new drug application, or NDA, with the U.S. Food & Drug Administration, or FDA, in mid-2022. SUL-DUR has been awarded Fast Track status designation providing potential eligibility for accelerated approval and priority review, if relevant criteria are met, following acceptance of our submission by the FDA. With the support of our partner Zai Lab (Shanghai) Co., Ltd. or Zai Lab (Nasdaq: ZLAB), we enrolled approximately 25% of the ATTACK trial in China and combined with the strength of the overall SUL-DUR

data set, we believe will also support a regulatory submission in China. Zai Lab has an exclusive license to develop and commercialize SUL-DUR in mainland China as well as the broader Asia-Pacific region.

Our second late-stage product candidate, zoliflodacin, is a novel orally administered molecule being developed for the treatment of uncomplicated gonorrhea. The bacterial pathogen responsible for gonorrhea is *Neisseria gonorrhoeae*, or *N. gonorrhoeae*, including multidrug-resistant strains. Intramuscular injections of ceftriaxone now represent the only U.S. Centers for Disease Control and Prevention, or CDC, recommended treatment option for the estimated 1.6 million annual cases of gonorrhea in the United States. We believe there is a growing unmet need for a single-dose oral antibiotic that will reliably treat patients with gonorrhea, including infections caused by multidrug-resistant strains of *N. gonorrhoeae*, which are emerging globally. The Phase 3 registration trial, initiated in September 2019, is sponsored by our nonprofit collaborator, the Global Antibiotic Research and Development Partnership, or GARDP, which as the sponsor is also responsible for all Phase 3 clinical trial and pharmaceutical development expenses. GARDP has commercial rights to zoliflodacin in up to 168 low- and select middle-income countries, while Entasis retains commercial rights in the major markets in North America, Europe and Asia-Pacific. Based on current enrollment rates, we anticipate the trial to be fully enrolled in 2023.

Our third product candidate is ETX0282CPDP which is a combination of a novel, oral BLI, ETX0282, with cefpodoxime proxetil or CPDP, which has the potential to address complicated urinary tract infections, or cUTIs, including those caused by multidrug-resistant *Enterobacteriaceae*. We believe there is a significant unmet need for new oral antibiotics to reliably treat the estimated 3 to 4 million patients diagnosed annually with cUTIs. We have reported preliminary Phase 1 trial results, and we are now seeking a partner to help further advance ETX0282CPDP through additional clinical trials. This program was previously supported by the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator program, or CARB-X.

We are also advancing the development of a novel class of antibiotics, non β-lactam inhibitors of penicillin-binding proteins, or NBPs. We believe NBPs constitute a potential new class of Gram-negative antibacterial agents that are designed to target a broad spectrum of multidrug resistant bacterial pathogens that overcome the main source of β-lactam resistance which is driven by β-lactamase activity. This novel class of agents is designed to potentially target a broad spectrum of multidrug resistant bacterial pathogens that are part of the CDC/World Health Organization, or WHO, list of high unmet medical need or ESKAPE pathogens. We selected ETX0462 as the initial clinical candidate for this program and with support from CARB-X we are currently working to complete additional pre-clinical activities to enable the program to advance into a Phase 1 clinical trial. In June 2020, we were awarded a contract from the National Institutes of Health, or NIH, to support research towards developing additional NBP molecules with expanded Gram-negative spectrum from this novel class. This research program, designated NBP2, is attempting to target *Klebsiella*, *Pseudomonas* and *E. coli* from the ESKAPE list of pathogens. In July 2021, we successfully completed the first milestones for the program and have been awarded the Option 1 Period of the program to proceed with further optimization, beginning August 1, 2021. Subject to achieving pre-defined milestones, the contract is expected to sufficiently fund activities to achieve submission of an Investigational New Drug, or IND, application to the FDA.

Since our inception in May 2015, we have devoted substantially all of our resources to organizing and staffing our company, business planning, raising capital, discovering product candidates and securing related intellectual property rights, conducting discovery and development activities for our programs and planning for potential commercialization. We do not have any products approved for sale and have not generated any revenue from product sales. As of December 31, 2021, we have funded our operations primarily with net cash proceeds of $104.2 million from the sale of our preferred stock, net cash proceeds of $65.6 million from the sale of common stock in our initial public offering, and net cash proceeds of $78.5 million from the sale of common stock, warrants and pre-funded warrants in private placements and at-the-market sales to certain investors in 2021 and 2020. We have also either directly received funding or financial commitments from, or have had our program activities conducted and funded by, the U.S. government through our arrangements with NIAID, CARB-X, and the U.S. Department of Defense, or DOD, and we have received non-profit awards from GARDP and upfront and milestone payments from our license and collaboration agreement with Zai Lab.

Funding Arrangements

NIH

In June 2020, we entered into a contract with NIAID, part of the NIH, with an effective date of July 1, 2020. The contract consists of an initial award of approximately $3.0 million, with the potential to increase it up to $15.5 million, that will be used to develop novel molecules from our NBP platform. In July 2021, we successfully completed the first milestones for the program associated with the initial award and have been awarded the Option 1 Period of the program to proceed with further optimization, beginning August 1, 2021. This option consists of any additional $2.9 million, bringing the total award to $5.9 million. Funding from the contract will support research towards developing molecules with expanded Gram-negative spectrum against antibiotic-resistant bacterial pathogens including *E. coli*, *Acinetobacter*, *Pseudomonas* and *Klebsiella*. Through December 31, 2021, we had received $3.2 million in payments and we have recorded $3.9 million of grant income under this funding arrangement.

CARB-X

In March 2017 and October 2017, we entered into funding arrangements with the Trustees of Boston University to utilize funds from the U.S. government, through the CARB-X program, for support of our ETX0282CPDP and ETX0462 programs. These funding arrangements could cover up to $18.5 million of our specified research expenditures from April 2017 through May 2023. Through December 31, 2021, we had received $12.6 million in payments and we have recorded $12.9 million of grant income under these funding arrangements. The remaining $5.6 million of grant income that could be recorded is related to our ETX0462 program.

License and Collaboration Agreements

GARDP

In July 2017, we entered into a collaboration agreement with GARDP for the development and commercialization of a product candidate containing zoliflodacin in certain countries. Under the terms of the

collaboration agreement, GARDP will fully fund the ongoing Phase 3 registration trial, including the manufacture and supply of the product candidate containing zoliflodacin, in uncomplicated gonorrhea.

Zai Lab

In April 2018, we entered into a license and collaboration agreement with Zai Lab pursuant to which Zai Lab licensed exclusive rights to durlobactam and SUL-DUR in the Asia-Pacific region. Under the terms of the agreement, Zai Lab will fund most of our registration trial costs in China for SUL-DUR, with the exception of Phase 3 patient drug supply of licensed product. As of December 31, 2021, we have received net payments of $15.8 million, representing the $5.0 million upfront payment, $7.0 million of milestone payments, $0.6 million of research support payments and $5.4 million of certain other reimbursable registration trial costs, less applicable taxes of $2.2 million, from Zai Lab and we have recognized revenue of $12.0 million under this agreement.

Components of Results of Operations

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our product discovery efforts and the development of our preclinical and clinical product candidates. These expenses include:

- employee-related expenses, including salaries and benefits, travel and stock-based compensation expense for employees engaged in research and development functions;
- fees paid to consultants for services directly related to our product development and regulatory efforts;
- expenses incurred under agreements with contract research organizations, or CROs, as well as contract manufacturing organizations, or CMOs, and consultants that conduct and provide supplies for our preclinical studies and clinical trials;
- costs associated with preclinical activities and development activities;
- costs associated with our technology and our intellectual property portfolio;
- costs related to compliance with regulatory requirements; and
- facilities-related expenses, which include allocated rent and maintenance of facilities and other operating costs.

Costs associated with research and development activities are expensed as incurred. Costs for certain development activities, such as clinical trials, are recognized based on an evaluation of the progress to completion of specific tasks using data such as patient enrollment, clinical site activations or other information provided to us by our vendors. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. Such amounts are recognized as an expense as the goods are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered, or the services rendered.

Our direct research and development expenses are tracked on a program-by-program basis for our product candidates and preclinical program and consist primarily of external costs, such as fees paid to outside consultants, CROs, CMOs and central laboratories in connection with our preclinical development, process development, manufacturing and clinical development activities. Our direct research and development expenses by program also

include fees incurred under service, license or option agreements. We do not allocate employee costs or facility expenses to specific programs because these costs are deployed across multiple programs and, accordingly, are not separately classified. We primarily use internal resources and our own employees to conduct our research and discovery as well as for managing our preclinical development, process development, manufacturing and clinical development activities.

To date, substantially all of our research and development expenses have been related to the preclinical and clinical development of our product candidates and preclinical programs. The following table shows our research and development expenses by development program and type of activity for the years ended December 31, 2021 and 2020:

	Year Ended December 31,	
	2021	2020
	(in thousands)	
Direct research and development expenses by program:		
SUL-DUR	$ 16,820	$ 23,356
ETX0462	2,271	1,968
ETX0282CPDP	130	160
Zoliflodacin	6	2
Other preclinical programs	1,126	822
Unallocated research and development expenses:		
Personnel related (including stock-based compensation)	14,464	12,383
Facilities, supplies and other	2,288	2,331
Total research and development expenses	$ 37,105	$ 41,022

Research and development activities are central to our business model. Product candidates in later 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. It is difficult to determine with certainty the duration and completion costs of our current or future preclinical programs and clinical trials of our product candidates, or if, when or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates.

The duration, costs and timing of clinical trials and development of our product candidates and preclinical program will depend on a variety of factors that include, but are not limited to, the following:

- the impact of COVID-19 on hospitals participating in the trials and their ability to focus on and direct resources to our trials;
- the number of trials required for approval and any requirement for extension trials;
- per-patient trial costs;
- the number of patients that participate in the trials;
- the number of sites included in the trials;
- the countries in which the trials are conducted;
- the length of time required to enroll eligible patients;
- the number of doses that patients receive;
- the drop-out or discontinuation rates of patients;

- potential additional safety monitoring or other studies requested by regulatory agencies;
- the duration of patient follow-up; and
- the efficacy and safety profiles of the product candidates.

Any changes in the outcome of any of these factors with respect to the development of our product candidates could mean a significant change in the costs and timing associated with the development of these product candidates. In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing and supply, and commercial viability. We will determine which programs to pursue and how much to fund each program based on the scientific and clinical success of each product candidate, as well as an assessment of each candidate's commercial potential.

General and Administrative Expenses

General and administrative expenses consist of salaries and benefits and stock-based compensation expense for personnel in executive, finance and administrative functions. General and administrative costs also include facilities-related costs not otherwise included in research and development expenses and professional fees for legal, patent, consulting, insurance, accounting and audit services.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research, development and commercialization activities of our product candidates. Additionally, if and when we believe a regulatory approval of a product candidate appears likely, we anticipate an increase in payroll and other employee-related expenses as a result of our preparation for commercial operations, especially as it relates to the sales and marketing functions for that product candidate.

Other Income

Grant Income

Grant income consists of income recognized in connection with grants we received under our funding arrangements with the Trustees of Boston University through the CARB-X program, as well as amounts received under our NIH contract. Grant income is recognized in the period during which the related specified expenses are incurred.

Interest Income

Interest income consists of interest earned on our cash and investment balances, which are primarily held in money market funds and U.S. Treasury Securities.

Results of Operations

Years Ended December 31, 2021 and 2020

The following table summarizes our results of operations for the years ended December 31, 2021 and 2020:

	Year Ended December 31,		$ Change
	2021	2020	
		(in thousands)	
Operating expenses:			
Research and development	37,105	41,022	(3,917)
General and administrative	15,212	13,209	2,003
Total operating expenses	52,317	54,231	(1,914)
Loss from operations	(52,317)	(54,231)	1,914
Other income:			
Grant income	5,163	3,562	1,601
Interest income	13	173	(160)
Total other income	5,176	3,735	1,441
Net loss	$ (47,141)	$ (50,496)	$ 3,355

Research and Development Expenses

Research and development expenses were $37.1 million for the year ended December 31, 2021, compared to $41.0 million for the year ended December 31, 2020. The decrease of $3.9 million was primarily due to a decrease of $6.5 million in clinical development expenses related to the advancement of SUL-DUR; offset in part by an increase of $2.1 million of personnel expenses associated with higher headcount, higher salaries and higher stock-based compensation expense resulting from options and restricted stock units granted during the year ended December 31, 2021, an increase of $0.3 million in preclinical and clinical development expenses related to the advancement of ETX0462 and an increase of $0.3 million in other preclinical programs. The decrease in preclinical and clinical development expenses of $6.5 million associated with SUL-DUR was primarily due to a decrease of $5.4 million in clinical trial costs, a decrease of $1.3 million in drug manufacturing costs, and a decrease of $0.4 million in commercial readiness activities; partially offset by an increase of $0.6 million in NDA filing support fees. The increase in clinical development expenses of $0.3 million associated with the advancement of ETX0462 was primarily due to an increase of $0.7 million in drug manufacturing costs, offset by a decrease of $0.4 million in toxicology studies.

General and Administrative Expenses

General and administrative expenses were $15.2 million for the year ended December 31, 2021, compared to $13.2 million for the year ended December 31, 2020. The increase of $2.0 million was driven by an increase of $1.0 million in personnel expenses associated with higher headcount and higher salaries, an increase of $0.6 million in professional expenses and an increase of $0.4 million in insurance expenses. The increase of $0.6 million in professional expenses was primarily due to an increase of $0.3 million in consulting expenses, an increase of $0.2 million in investor and public relations expenses and an increase of $0.1 million in legal expenses.

Other Income

Other income was $5.2 million for the year ended December 31, 2021, compared to $3.7 million for the year ended December 31, 2020. The increase of $1.4 million was due to an increase in grant income of $1.6 million from our agreements with CARB-X and NIH; offset by a decrease in interest income of $0.2 million.

Liquidity and Capital Resources

Overview

As of December 31, 2021, we had cash and cash equivalents of $32.3 million. We have funded our operations to date with the proceeds from equity securities offerings. In addition, we also have received funding or financial commitments from, or have had our program activities conducted and funded by, the U.S. government through arrangements with NIAID, CARB-X, NIH and the U.S. Department of Defense, and have received non-profit awards from GARDP and upfront milestone and cost reimbursement payments from Zai Lab.

Going Concern

Since our inception, we have incurred recurring losses and negative cash flows from operations. Our net loss was $47.1 million for the year ended December 31, 2021 and $50.5 million for the year ended December 31, 2020. As of December 31, 2021, we had an accumulated deficit of $231.6 million. We anticipate that a substantial portion of our capital resources and efforts in the foreseeable future will be focused on completing the necessary development, obtaining regulatory approval and preparing for potential commercialization of our product candidates. Based on our current operating plan, we do not believe that our existing cash and cash equivalents, including the $15.0 million received from Innoviva in February 2022 as part of the securities purchase agreement described in further detail below, will be sufficient to fund our operating expenses and capital expenditure requirements through the remainder of 2022. However, we believe it will be sufficient to fund our operating expenses and capital expense requirements through the end of the third quarter of 2022.

These conditions and events raise substantial doubt about our ability to continue as a going concern for the one-year period following the issuance of our financial statements for the year ended December 31, 2021. To finance our operations beyond this point, we will need to raise substantial additional capital or effectively implement cost reductions, neither of which can, be assured. To the extent that we raise additional capital through future equity offerings, the ownership interest of common stockholders will be further diluted, which dilution may be significant. See Note 1, *Organization and Description of Business*, and Note 8, *Stockholders' Equity and Stock Based Compensation Expense*, in the accompanying notes to our unaudited consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for additional information on our assessment. If we are not able to secure adequate additional funding in future periods, we may make reductions in certain expenditures, which may include suspending or curtailing planned activities and delaying, or reducing the scope of, suspending or eliminating one or more research and development programs or commercialization efforts. Our 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 we will continue as a going concern and that contemplates the realization of assets and satisfaction of liabilities and commitments in the ordinary course of business.

Funding Requirements

Our primary uses of capital are, and we expect will continue to be, compensation and related expenses, third-party clinical research and development services, laboratory and related supplies, manufacturing development costs, legal and other regulatory expenses and general administrative costs.

The successful development of our product candidates is highly uncertain. At this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the clinical development of our product candidates and obtain regulatory approvals. We are also unable to predict when, if ever, net cash inflows will commence from product sales. This is due to the numerous risks and uncertainties associated with developing drugs, including, among others, the uncertainty of:

- the unpredictable duration and economic impact of the COVID-19 pandemic;
- successful enrollment in, and completion of clinical trials;

- performing preclinical studies and clinical trials in compliance with requirements of the FDA, the EMA, or any comparable regulatory authority;
- the ability of collaborators to manufacture sufficient quantity of product for development, clinical trials or potential commercialization;
- obtaining marketing approvals with labeling for sufficiently broad patient populations and indications, without unduly restrictive distribution limitations or safety warnings, such as black box warnings or a risk evaluation and mitigation strategies program;
- obtaining and maintaining patent, trademark and trade secret protection and regulatory exclusivity for our product candidates;
- making arrangements with third parties for manufacturing capabilities;
- launching commercial sales of products, if and when approved, whether alone or in collaboration with others;
- acceptance of the therapies, if and when approved, by physicians, patients and third-party payors;
- competing effectively with other therapies;
- obtaining and maintaining healthcare coverage and adequate reimbursement;
- protecting our rights in our intellectual property portfolio; and
- maintaining a continued acceptable safety profile of our drugs following approval.

A change in the outcome of any of these variables with respect to the development of any of our product candidates would significantly change the costs and timing associated with the development of that product candidate.

We will not generate revenue from product sales unless and until we or a collaborator successfully complete clinical development and obtain regulatory approval for our current and future product candidates. If we obtain regulatory approval for any of our product candidates that we ultimately decide to commercialize on our own, we will incur significant expenses related to commercialization, including developing our internal commercialization capability to support product sales, marketing and distribution.

As a result, we will need substantial additional funding to support our continuing operations and to pursue our growth strategy. Until such time, if ever, when we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings and potential collaboration, license and development agreements. 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.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to 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 drug development or future commercialization efforts or grant rights to a third party to develop and market product candidates that we would otherwise prefer to develop and market ourselves. Our failure to raise capital as and when needed would compromise our ability to pursue our business strategy.

We will also continue to incur costs as a public company that we did not incur or incurred at lower rates prior to our initial public offering, including increased fees payable to the nonemployee members of our board of directors, increased personnel costs, increased director and officer insurance premiums, audit and legal fees, investor relations fees and expenses for compliance with public-company reporting requirements under the Exchange Act and rules implemented by the SEC and Nasdaq.

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, we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

At-the-Market Facility

In August 2021, we entered into a Controlled Equity Offering Sales Agreement, or Sales Agreement, with Cantor Fitzgerald & Co, or Cantor, for the offer and sale of up to $17.5 million of its common stock at the then current market prices in amounts to be determined from time to time. On October 21, 2021, the Company sold an aggregate of 200,000 shares of common stock at a sale price of $3.25 per share, for gross proceeds of $0.7 million. Proceeds, net of fees, were $0.6 million.

Innoviva, Inc. Securities Purchase Agreement

On May 3, 2021, we entered into a securities purchase agreement, or the Third Securities Purchase Agreement, with a subsidiary Innoviva, Inc., or Innoviva, pursuant to which we agreed to issue and sell to the Innoviva subsidiary, in a private placement up to 10,000,000 newly issued shares of our common stock at $2.00 per share and warrants to purchase up to 10,000,000 shares of common stock, each with an exercise price per share of $2.00, collectively the Third Private Placement. The warrants will be exercisable immediately and will have a five-year term.

The Third Private Placement occurred in two tranches. At the closing of the first tranche, or the First Closing, which occurred on May 3, 2021, Innoviva purchased 3,731,025 shares of common stock and warrants to purchase 3,731,025 shares of common stock, for aggregate gross proceeds of $7.5 million. At the closing of the second tranche, or the Second Closing, which occurred on June 30, 2021, Innoviva purchased the remaining 6,268,975 shares of common stock and warrants to purchase 6,268,975 shares of common stock for aggregate gross proceeds of $12.5 million.

As of December 31, 2021, Innoviva owns approximately 59.9% of our outstanding common stock, without giving effect to the potential exercise of warrants. On February 1, 2022, our Board of Directors received a preliminary, non-binding proposal from Innoviva to acquire all the outstanding equity securities of the Company that are not currently owned by Innoviva for a per share consideration of $1.80 payable in cash. The offer letter delivered by Innoviva to our Board of Directors is publicly available in the Schedule 13D amendment dated February 1, 2022, filed by Innoviva with the SEC. Our Board of Directors, which does not include any members appointed by or affiliated with Innoviva, has retained MTS Health Partners, L.P. and Covington & Burling, LLP to explore alternatives and to assist the board of directors in its evaluation of the proposal consistent with fiduciary duties.

On February 17, 2022, we entered into a securities purchase agreement, or the Fourth Securities Purchase Agreement, with a subsidiary of Innoviva, pursuant to which we issued and sold to Innoviva, in a private placement which closed on February 18, 2022, a convertible promissory note having a principal amount of $15.0 million, or Convertible Note. The Convertible Note is convertible at maturity at the election of us or Innoviva into shares of our common stock at a conversion price of $1.48 per share of common stock and warrants to purchase an equal number of shares of common stock with an exercise price of $1.48 per share of common stock, or the Warrants. The Convertible Note will also be convertible at the option of Innoviva if we engage in certain capital markets transactions, asset sales or royalty transactions. If we are acquired prior to the maturity date of the Convertible Note, the Convertible Note will be payable in cash at the time of such acquisition. The Convertible Note will mature on August 18, 2022 and bears interest at a rate of 0.59% per annum to, but excluding, the date of repayment or conversion of the Convertible Note. From and

including the date of maturity, if not converted, the Convertible Note will bear interest at a rate of 10.00% per annum to, but excluding, the date of repayment or conversion of the Convertible Note.

The Convertible Note and the Warrants will have provisions that preclude conversion or exercise, respectively, if such conversion or exercise would result in the issuance of more than 19.99% of the our currently outstanding common stock in the aggregate prior to obtaining stockholder approval.

Registration Rights Agreement

On February 18, 2022, we and Innoviva entered into a registration rights agreement, or the Registration Rights Agreement, pursuant to which, among other things, we must prepare and file with the Securities and Exchange Commission, or the SEC, a registration statement with respect to the resale of shares of common stock and the warrants issuable upon conversion of the Convertible Note and shares of common stock issuable upon exercise of the Warrants.

Cash Flows

The following table summarizes our cash flows for the periods presented (in thousands):

	Year Ended December 31,	
	2021	2020
Net cash used in operating activities	$ (42,972)	$ (45,426)
Net cash (used in) provided by investing activities	(70)	24,982
Net cash provided by financing activities	22,102	57,657
Net (decrease) increase in cash and cash equivalents	$ (20,940)	$ 37,213

Operating Activities

During the year ended December 31, 2021, operating activities used $43.0 million of cash, resulting from our net loss of $47.1 million partially offset by non-cash charges of $4.1 million. Non-cash charges were primarily comprised of stock-based compensation expense of $4.0 million.

During the year ended December 31, 2020, operating activities used $45.4 million of cash, resulting from our net loss of $50.5 million partially offset by non-cash charges of $3.1 million and net cash provided by changes in operating assets and liabilities of $2.0 million. Net cash provided by changes in operating assets and liabilities for the year ended December 31, 2020 consisted primarily of a $1.9 million decrease in other assets, a $1.0 million increase in accrued expenses and other liabilities, and a $0.4 million decrease in prepaid expenses. These were partially offset by a $0.7 million increase in grants receivable and a $0.6 million decrease in accounts payable.

Investing Activities

During the year ended December 31, 2021, net cash used in investing activities was $70,000, consisting of purchases of property and equipment.

During the year ended December 31, 2020, net cash provided by investing activities was $25.0 million, consisting primarily of proceeds from maturities of short-term investments.

Financing Activities

During the year ended December 31, 2021, net cash provided by financing activities was $22.1 million, which consisted of $20.0 million of proceeds from the issuance of common stock and warrants in the Third Private Placement, net of financing costs, $1.8 million of proceeds from the exercise of warrants, and $0.4 million of proceeds from the sale of common stock related to our at-the-market offering.

During the year ended December 31, 2020, net cash provided by financing activities was $57.7 million, which consisted of proceeds from the issuance of common stock and warrants in the First Private Placement and Second Private Placement, net of issuance costs.

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 SEC.

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, revenues and expenses, and the disclosure of contingent assets and liabilities in our consolidated 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 , *Summary of Significant Accounting Policies*, in the accompanying notes 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.

Research and Development Expenses

All research and development expenses are expensed as incurred. Research and development expenses comprise costs incurred in performing research and development activities, including compensation, benefits and other employee costs; equity-based compensation expense; laboratory and clinical supplies and other direct expenses; facilities expenses; overhead expenses; fees for contractual services, including preclinical studies, clinical trials, clinical manufacturing and raw materials; and other external expenses. Nonrefundable advance payments for research and development activities are capitalized and expensed over the related service period or as goods are received. When third-party service providers' billing terms do not coincide with our period-end, we are required to make estimates of our obligations to those third parties, including clinical trial costs, contractual service costs and costs for supply of our drug candidates, incurred in a given accounting period and record accruals at the end of the period. We base our estimates on our knowledge of the research and development programs, services performed for the period and the expected duration of the third-party service contract, where applicable.

Recent Accounting Pronouncements

Refer to Note 2, *Summary of Significant Accounting Policies*, in the accompanying notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for a discussion of recent accounting pronouncements.

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.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

As a smaller reporting company, we are not required to provide disclosure for this Item.

Item 8. Financial Statements and Supplementary Data

Our financial statements, together with the report of our independent registered public accounting firm, appear in this Annual Report on Form 10-K beginning on page F-1.

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

We maintain "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, 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.

Our management, with the participation of our Chief Executive Officer and Vice President Corporate Controller, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2021. Based on the evaluation of our disclosure controls and procedures as of December 31, 2021, our Chief Executive Officer and Vice President Corporate Controller concluded that, as of such date, our disclosure controls and procedures were effective at a reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rule 13a-15(f) and 15d-15(f) under the Exchange Act.

Our management conducted an assessment of the effectiveness of our internal control over financial reporting based on the criteria set forth in "Internal Control-Integrated Framework (2013)" issued by the Committee of Sponsoring Organizations of the Treadway Commission, or COSO. Based on this assessment, management concluded that, as of December 31, 2021, our internal control over financial reporting was effective based on criteria established in the COSO 2013 framework.

Attestation Report of the Registered Public Accounting Firm

This Annual Report on Form 10-K does not include an attestation report of our registered public accounting firm on internal control over financial reporting due to an exemption established by the JOBS Act for "emerging growth companies."

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting that occurred during our most recent fiscal quarter that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers, and Corporate Governance

The information required by this item will be included in the information set forth in the sections titled “Proposal 1 – Election of Directors,” “Executive Officers,” and “Information Regarding the Board and Corporate Governance” and “Delinquent Section 16(a) Reports,” if applicable, in our definitive proxy statement to be filed with the SEC with respect to our 2021 Annual Meeting of Stockholders, or our Proxy Statement, and is incorporated by reference.

Item 11. Executive Compensation

The information required by this item will be included in the information set forth in the section titled “Executive Officer and Director Compensation” in our Proxy Statement and is incorporated by reference.

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

The information required by this item will be included in the information set forth in the section titled “Security Ownership of Certain Beneficial Owners and Management” and “Equity Compensation Plan Information” in our Proxy Statement and is incorporated by reference.

Item 13. Certain Relationships and Related Transactions and Director Independence

The information required by this item will be included in the information set forth in the section titled “Transactions with Related Persons” and “Information regarding the Board and Corporate Governance – Board Independence” in our Proxy Statement and is incorporated by reference.

Item 14. Principal Accounting Fees and Services

The information required by this item will be included in the information set forth in the section titled “Independent Registered Public Accounting Firm Fees” contained in Proposal 2 in our Proxy Statement and is incorporated by reference.

PART IV

Item 15. Exhibits, Financial Statements Schedules

(a)(1) Financial Statements.

The response to this portion of Item 15 is set forth under Item 8 hereof.

(a)(2) Financial Statement Schedules.

All schedules have been omitted because they are not required or because the required information is given in the Financial Statements or Notes thereto.

(a)(3) Exhibits.

The exhibits listed below are filed as part of this Form 10-K other than Exhibit 32.1, which shall be deemed furnished.

Number	Description
3.1	Amended and Restated Certificate of Incorporation of the Company (incorporated herein by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on September 28, 2018).
3.1.1	Certificate of Amendment to the Amended and Restated Certificate of Incorporation of the Company (incorporated herein by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on June 11, 2020).
3.2	Amended and Restated Bylaws of the Company (incorporated herein by reference to Exhibit 3.2 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on September 28, 2018).
4.1	Description of the Company's Securities Registered Pursuant to Section 12 of the Securities Exchange Act of 1934 (incorporated herein by reference to Exhibit 4.3 to the Company's Annual Report on Form 10-K (File No. 001-38670) filed with the SEC on March 11, 2020).
4.2	Form of Common Stock Certificate of the Company (incorporated herein by reference to Exhibit 4.1 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
4.3	Registration Rights Agreement, by and between the Company and Innoviva, Inc., dated April 22, 2020 (incorporated herein by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on April 22, 2020).
4.4	Form of Warrant Certificate (incorporated herein by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on April 13, 2020).
4.5	Registration Rights Agreement, by and between the Company and the Investors named therein, dated September 1, 2020 (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on September 1, 2020).
4.6	Form of Common Stock Purchase Warrant (incorporated herein by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on September 1, 2020).
4.7	Form of Pre-Funded Common Stock Purchase Warrant (incorporated herein by reference to Exhibit 4.2 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on September 1, 2020).
4.8	Registration Rights Agreement, by and between the Company and Innoviva Strategic Opportunities LLC, dated May 3, 2021 (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on May 3, 2021).

4.9	Form of Common Stock Purchase Warrant (incorporated herein by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on May 3, 2021).
4.10	Convertible Promissory Note, dated February 18, 2022 (incorporated herein by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on February 18, 2022).
4.11	Form of Warrant Certificate (incorporated herein by reference to Exhibit 4.2 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on February 18, 2022).
10.1+	Form of Indemnification Agreement by and between the Company and each of its directors and officers (incorporated herein by reference to Exhibit 10.16 to the Company's Registration Statement on Form S-1/A (File No. 333-226920), filed with the SEC on September 18, 2018).
10.2+	Forms of Stock Option Grant Notice and Stock Option Agreement under the 2018 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.10 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
10.3+	2018 Employee Stock Purchase Plan (incorporated herein by reference to Exhibit 10.4 to the Company's Quarterly Report on Form 10-Q (File No. 001-38670), filed with the SEC on November 14, 2018).
10.4+	Amended and Restated Stock Incentive Plan (incorporated herein by reference to Exhibit 10.6 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
10.5+	Form of Nonqualified Stock Option Agreement (Senior Management) under the Amended and Restated Stock Incentive Plan (incorporated herein by reference to Exhibit 10.7 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
10.6+	Form of Incentive Stock Option Agreement (Senior Management) under the Amended and Restated Stock Incentive Plan (incorporated herein by reference to Exhibit 10.8 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
10.7+	Employment Agreement between the Company and Manoussos Perros, effective September 25, 2018 (incorporated herein by reference to Exhibit 10.13 to the Company's Registration Statement on Form S-1/A (File No. 333-226920), filed with the SEC on September 18, 2018).
10.8+	Employment Agreement between the Company and Ruben Tommasi, effective September 25, 2018 (incorporated herein by reference to Exhibit 10.12 to the Company's Annual Report on Form 10-K (File No. 001-38670), filed with the SEC on March 29, 2019).
10.9†	Amended and Restated Business Transfer and Subscription Agreement, dated March 29, 2016, by and among AstraZeneca AB, AstraZeneca UK Limited, AstraZeneca Pharmaceuticals LP, and the Company (incorporated herein by reference to Exhibit 10.1 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).

10.10†	Amendment to Amended and Restated Business Transfer and Subscription Agreement, dated August 28, 2017, by and among AstraZeneca AB, AstraZeneca UK Limited, AstraZeneca Pharmaceuticals LP, and the Company (incorporated herein by reference to Exhibit 10.2 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
10.11†	Amendment No. 2 to Amended and Restated Business Transfer and Subscription Agreement, dated January 30, 2018, by and among AstraZeneca AB, AstraZeneca UK Limited, AstraZeneca Pharmaceuticals LP, and the Company (incorporated herein by reference to Exhibit 10.3 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
10.12†	Collaboration Agreement, dated July 4, 2017, by and between the Drugs for Neglected Diseases initiative, acting through the Global Antibiotic Research and Development Partnership, and the Company (incorporated herein by reference to Exhibit 10.4 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
10.13	Novation of Contract, dated January 11, 2019, by and between the Global Antibiotic Research and Development Partnership and the Company (incorporated herein by reference to Exhibit 10.17 to the Company's Annual Report on Form 10-K (File No. 001-38670), filed with the SEC on March 29, 2019).
10.14†	License and Collaboration Agreement, dated April 25, 2018, by and between Zai Lab (Shanghai) Co., Ltd. and the Company (incorporated herein by reference to Exhibit 10.5 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
10.15+	Amended Non-Employee Director Compensation Policy, as amended December 6, 2019 (incorporated herein by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q (File No. 001-38670), filed with the SEC on August 6, 2020).
10.16+	Special Bonus Award Memorandum, dated May 15, 2020 (incorporated herein by reference to Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q (File No. 001-38670), filed with the SEC on August 6, 2020).
10.17	Form of Voting Agreement (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on April 13, 2020).
10.18	Investor Rights Agreement, by and between the Company and Innoviva, Inc., dated April 22, 2020 (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on April 22, 2020).
10.19+	First Amendment to 2018 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q (File No. 001-38670), filed with the SEC on August 6, 2020).
10.20+	Form of Restricted Stock Unit Grant Notice (Time-Based) (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on November 6, 2020).

10.21+	Form of Restricted Stock Unit Grant Notice (Performance-Based) (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on November 6, 2020).
10.22+	Form of Restricted Stock Unit Grant Agreement (incorporated herein by reference to Exhibit 10.3 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on November 6, 2020).
10.23+	Form of Executive Officer Employment Agreement (incorporated herein by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q (File No. 001-38670), filed with the SEC on May 7, 2020).
10.24	Second Amended Non-Employee Director Compensation Policy, as amended January 1, 2022
10.25	Amendment to Incentive Stock Option Agreement for employees under the 2015 Stock Incentive Plan
10.26	Amendment to Incentive Stock Option Agreement for senior management under the 2015 Stock Incentive Plan
10.27	Amendment to Nonqualified Stock Option Agreement for employees under the 2015 Stock Incentive Plan
10.28	Amendment to Nonqualified Stock Option Agreement for senior management under the 2015 Stock Incentive Plan
10.29	Amendment to Stock Option Agreements under the 2018 Equity Incentive Plan
10.30	Amendment to Restricted Stock Unit Agreements under the 2018 Equity Incentive Plan
10.31	Amended Stock Option Agreement under the 2018 Equity Incentive Plan
10.32	Amended Restricted Stock Unit Agreement under the 2018 Equity Incentive Plan
10.33	Form of Retention Bonus Award Memo
10.34	Securities Purchase Agreement, dated February 17, 2022, by and between the Company and Innoviva (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on February 18, 2022).
10.35	Registration Rights Agreement, dated February 18, 2022 by and between the Company and Innoviva (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on February 18, 2022).
10.36+	2018 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q (File No. 001-38670), filed with the SEC on November 14, 2018).
21.1	Subsidiaries of Entasis Therapeutics Holdings Inc.
23.1	Consent of Independent Registered Public Accounting Firm.

24.1	Power of Attorney (included on the signature page to this report).
31.1	Certification of Chief 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.
31.2	Certification of Vice President Corporate Controller 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.
32.1*	Certification of Chief Executive Officer and Vice President Corporate Controller Pursuant to 18 U.S.C. Section 1350, as adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	Inline XBRL Instance Document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	The cover page from the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2020 formatted in inline XBRL (included in Exhibit 101).

* Furnished herewith and not deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and shall not be deemed to be incorporated by reference into any filing under the Securities Act or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

\+ Indicates a management contract or compensatory plan.

† Confidential treatment has been granted with respect to portions of this exhibit (indicated by asterisks) and those portions have been separately filed with the Securities and Exchange Commission.

Item 16. Form 10-K Summary

Not applicable.

SIGNATURES

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

ENTASIS THERAPEUTICS HOLDINGS INC.

Date: March 3, 2022

By: /s/ Manoussos Perros
Manoussos Perros, Ph.D.
President and Chief Executive Officer

POWER OF ATTORNEY

Each person whose individual signature appears below hereby authorizes and appoints Manoussos Perros, Ph.D. and Kristie Wagner and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this report on Form 10-K, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his or her substitute or substitutes may lawfully do or cause to be done by virtue thereof.

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

Signature	Title	Date
/s/ Manoussos Perros Manoussos Perros, Ph.D.	President, Chief Executive Officer and Director *(Principal Executive Officer)*	March 3, 2022
/s/ Kristie Wagner Kristie Wagner	Vice President Corporate Controller *(Principal Financial and Accounting Officer)*	March 3, 2022
/s/ David Meek David Meek	Chairman of the Board	March 3, 2022
/s/ Heather Behanna Heather Behanna, Ph.D.	Director	March 3, 2022
/s/ David C. Hastings David C. Hastings	Director	March 3, 2022
/s/ Heather Preston Heather Preston, M.D.	Director	March 3, 2022
/s/ Howard Mayer Howard Mayer, M.D.	Director	March 3, 2022

ENTASIS THERAPEUTICS HOLDINGS INC.
Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
Entasis Therapeutics Holdings Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Entasis Therapeutics Holdings Inc. and subsidiaries (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the years then ended, 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, 2021 and 2020, and the results of its operations and its cash flows for each of the years then ended, in conformity with U.S. generally accepted accounting principles.

Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the consolidated financial statements, the Company has incurred recurring net losses and negative cash flows from its operations since inception that raise substantial doubt about its ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

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. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

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 LLP

We have served as the Company's auditor since 2017.

Boston, Massachusetts
March 3, 2022

ENTASIS THERAPEUTICS HOLDINGS INC.
CONSOLIDATED BALANCE SHEETS
(in thousands, except share and per share data)

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 32,307	$ 53,247
Grants receivable	1,258	1,890
Prepaid expenses	5,754	4,160
Other current assets	496	835
Total current assets	39,815	60,132
Property and equipment, net	198	222
Operating lease right-of-use assets	604	1,141
Other assets	303	63
Total assets	$ 40,920	$ 61,558
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 1,183	$ 660
Accrued expenses and other current liabilities	8,525	7,905
Total current liabilities	9,708	8,565
Operating lease liabilities, net of current portion	—	704
Total liabilities	9,708	9,269
Commitments (Notes 4 and 10)		
Stockholders' equity:		
Common stock, par value $0.001; 125,000,000 shares authorized and 47,851,779 and 36,637,357 shares issued and outstanding as of December 31, 2021 and December 31, 2020, respectively	48	37
Additional paid-in capital	262,760	236,707
Accumulated deficit	(231,596)	(184,455)
Total stockholders' equity	31,212	52,289
Total liabilities and stockholders' equity	$ 40,920	$ 61,558

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

ENTASIS THERAPEUTICS HOLDINGS INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(in thousands, except share and per share data)

	Year Ended December 31,	
	2021	2020
Operating expenses:		
Research and development	$ 37,105	$ 41,022
General and administrative	15,212	13,209
Total operating expenses	52,317	54,231
Loss from operations	(52,317)	(54,231)
Other income:		
Grant income	5,163	3,562
Interest income	13	173
Total other income	5,176	3,735
Net loss and comprehensive loss	$ (47,141)	$ (50,496)
Net loss per share —basic and diluted	$ (1.09)	$ (2.10)
Weighted average common stock outstanding—basic and diluted	43,340,826	24,060,615

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

ENTASIS THERAPEUTICS HOLDINGS INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands, except share data)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount			
Balances as of December 31, 2019	13,291,563	$ 13	$ 176,103	$ (133,959)	$ 42,157
Stock-based compensation expense			2,951		2,951
Sale of common stock and warrants in private placements, net of issuance costs	22,183,878	22	57,653		57,675
Exercise of warrants	1,161,916	2			2
Net loss				(50,496)	(50,496)
Balances as of December 31, 2020	36,637,357	37	236,707	(184,455)	52,289
Stock-based compensation expense	—	—	4,023	—	4,023
Sale of common stock and warrants in private placement, net of issuance costs	10,000,000	10	19,941	—	19,951
Exercise of warrants	672,897	1	1,799	—	1,800
Sale of common stock related to at-the-market offering, net of issuance costs	200,000	—	290	—	290
Issuance of common stock upon the vesting of restricted stock units	341,525	—	—	—	—
Net loss	—	—	—	(47,141)	(47,141)
Balances as of December 31, 2021	47,851,779	$ 48	$ 262,760	$ (231,596)	$ 31,212

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

ENTASIS THERAPEUTICS HOLDINGS INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	Year Ended December 31,	
	2021	2020
Cash flows from operating activities:		
Net loss	$ (47,141)	$ (50,496)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	104	141
Stock-based compensation expense	4,023	2,951
Amortization and accretion of investments	—	(37)
Changes in operating assets and liabilities:		
Grants receivable	632	(658)
Prepaid expenses	(1,594)	400
Other assets	636	1,881
Accounts payable	513	(644)
Accrued expenses and other liabilities	(145)	1,036
Net cash used in operating activities	(42,972)	(45,426)
Cash flows from investing activities:		
Purchases of property and equipment	(70)	(18)
Proceeds from maturities of short-term investments	—	25,000
Net cash (used in) provided by investing activities	(70)	24,982
Cash flows from financing activities:		
Proceeds from the sale of common stock and warrants in private placements, net of issuance costs	19,951	57,657
Proceeds from the exercise of warrants	1,800	—
Proceeds from the sale of common stock related to at-the-market offering, net of issuance costs	351	—
Net cash provided by financing activities	22,102	57,657
Net (decrease) increase in cash and cash equivalents	(20,940)	37,213
Cash and cash equivalents at beginning of the year	53,247	16,034
Cash and cash equivalents at end of the year	$ 32,307	$ 53,247
Supplemental disclosure of non-cash investing and financing activities:		
Financing costs included in accrued expenses	$ 61	$ —
Purchases of property and equipment in accounts payable	$ 10	$ —

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

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Description of Business

Entasis Therapeutics Holdings Inc., or Entasis, or the Company, is an advanced, late clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of targeted antibacterial products that address high unmet medical needs to treat serious infections caused by multidrug-resistant pathogens. The Company has four subsidiaries: Entasis Therapeutics Limited; Entasis Therapeutics Inc.; Entasis Therapeutics Security Corporation; and Entasis Therapeutics (Ireland) Limited.

On April 12, 2020, the Company entered into a securities purchase agreement, or the First Securities Purchase Agreement, with Innoviva Inc., or Innoviva, pursuant to which the Company issued and sold to Innoviva, in a private placement, 14,000,000 newly issued shares of common stock of the Company at $2.50 per share, and warrants to purchase up to 14,000,000 shares of common stock with an exercise price per share of $2.50, resulting in an aggregate gross purchase price of approximately $35.0 million, collectively, the First Private Placement. As a result of the transaction, Innoviva acquired control of the Company, owning approximately 51.3% of the Company's common stock without giving effect to the potential exercise of its warrants.

On August 27, 2020, the Company entered into another securities purchase agreement, or the Second Securities Purchase Agreement, with the purchasers named therein, or the Investors, which included existing stockholder Innoviva. Pursuant to the Second Securities Purchase Agreement, the Company issued and sold to the Investors in a private placement (i) 8,183,878 newly issued shares of common stock of the Company at $2.675 per share, (ii) warrants to purchase an aggregate of 9,345,794 shares of common stock with an exercise price of $2.675, and (iii) pre-funded warrants, in lieu of common stock, to purchase an aggregate of 1,161,916 shares of common stock with an exercise price of $0.001 per share, resulting in aggregate gross proceeds of approximately $25.0 million, which is referred to collectively as the Second Private Placement. The closing of the Second Private Placement occurred on September 1, 2020. As a result of the transaction, Innoviva owned approximately 52.6% of the Company's common stock without giving effect to the potential exercise of its warrants.

On May 3, 2021, the Company entered into a securities purchase agreement, or the Third Securities Purchase Agreement, with a subsidiary of Innoviva, pursuant to which the Company agreed to issue and sell to Innoviva, in a private placement up to 10,000,000 newly issued shares of common stock of the Company at $2.00 per share and warrants to purchase up to 10,000,000 shares of common stock with an exercise price per share of $2.00, collectively, the Third Private Placement. The warrants were exercisable immediately and have a five-year term.

The Third Private Placement occurred in two tranches. At the closing of the first tranche, or the First Closing, which occurred on May 3, 2021, Innoviva purchased 3,731,025 shares of common stock and warrants to purchase up to 3,731,025 shares of common stock, for an aggregate purchase price of approximately $7.5 million. At the closing of the second tranche, or the Second Closing, which occurred on June 11, 2021, Innoviva purchased the remaining 6,268,975 shares of common stock and warrants to purchase up to 6,268,975 shares of common stock, for an aggregate purchase price of approximately $12.5 million. As a result of these transactions, as of December 31, 2021, Innoviva owned approximately 59.9% of the Company's common stock without giving effect to the potential exercise of the warrants. If Innoviva were to exercise all of its warrants, as of December 31, 2021 Innoviva would have held approximately 74.9% of the Company's outstanding common stock.

On February 17, 2022, the Company entered into a securities purchase agreement, or Fourth Securities Purchase Agreement with a subsidiary of Innoviva, pursuant to which the Company issued and sold to Innoviva, in a private placement which closed on February 18, 2022, a convertible promissory note having a principal amount of $15.0 million. This transaction is described in further detail in Note 16 – *Subsequent Events*.

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

Going Concern

Since its inception, the Company has incurred recurring net losses and negative cash flows from its operations. The Company has financed its operations primarily with proceeds from the sale of preferred stock, common stock, warrants and pre-funded warrants. As of December 31, 2021, the Company had cash and cash equivalents of $32.3 million.

The Company follows the provisions of Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 205-40, *Presentation of Financial Statements — Going Concern*, or ASC 205-40, which requires management to assess the Company's ability to continue as a going concern for one year after the date the consolidated financial statements are issued.

Based on the Company's available cash resources, the Company believes its existing cash and cash equivalents, including the $15.0 million received from Innoviva as part of the Fourth Securities Purchase Agreement, will enable it to fund its operating expenses and capital requirements through the end of the third quarter of 2022. Accordingly, management does not expect that its existing cash and cash equivalents as of December 31, 2021 will be sufficient to enable the Company to fund its operating expenses and capital expenditure requirements through the first quarter of 2023. Management has concluded that substantial doubt exists about the Company's ability to continue as a going concern for one year from the date these financial statements are issued. The Company expects to seek additional funding to sustain its future operations and while the Company has successfully raised capital in the past, the ability to raise capital in future periods is not assured. If the Company is not able to secure adequate additional funding in future periods, the Company may make reductions in certain expenditures. This may include suspending or curtailing planned activities. The Company may also have to delay, reduce the scope of, suspend or eliminate one or more research and development programs or its commercialization efforts. A failure to raise substantial additional funding or effectively implement cost reductions could harm the Company's business, results of operations and future prospects.

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

Risks and Uncertainties

As of December 31, 2021, the Company had $32.3 million in cash and cash equivalents, and an accumulated deficit of $231.6 million. Since its inception through December 31, 2021, the Company has funded its operations primarily with proceeds from the sale of preferred stock, common stock, warrants and pre-funded warrants. The Company also has either directly received funding or financial commitments from, or has had its program activities conducted and funded by, United States government agencies, non-profit entities and the collaboration agreement with Zai Lab (Shanghai), Co., Ltd., or Zai Lab. In the absence of positive cash flows from operations, the Company is highly dependent on its ability to find additional sources of funding in the form of debt, equity financing, strategic collaborations, or partnerships. If the Company raises additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, it may be required to relinquish valuable rights to its technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable. If the Company is unable to raise additional funds through equity or debt financings when needed, it may be required to delay, limit, reduce or terminate drug development or future commercialization efforts or grant rights to a third party to develop and market product candidates. The Company's failure to raise capital as and when needed would compromise its ability to pursue its business strategy.

As a late clinical-stage company, Entasis is subject to a number of risks common to other life science companies, including, but not limited to, raising additional capital, development by its competitors of new technological innovations, risk of failure in preclinical and clinical studies, safety and efficacy of its product candidates in clinical trials, the risk of relying on external parties such as contract research organizations and contract manufacturing organizations, the regulatory approval process, market acceptance of the Company's products once approved, lack of

marketing and sales history, dependence on key personnel and protection of proprietary technology. The Company's therapeutic programs are currently pre-commercial, spanning discovery through late-stage development and will require additional research and development efforts, including the completion of Phase 3 registration trials and regulatory approval, prior to commercialization of any product candidates. These efforts require significant amounts of additional capital, adequate personnel, infrastructure, and extensive compliance-reporting capabilities. There can be no assurance that the Company's research and development will be successfully completed, that adequate protection for the Company's intellectual property will be obtained, that any products developed will obtain necessary regulatory approval or that any approved products will be commercially viable. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will generate revenue from product sales. The Company may never achieve profitability, and unless and until it does, it will continue to need to raise additional capital or obtain financing from other sources, such as strategic collaborations or partnerships.

The COVID-19 pandemic has, and will likely continue to have, a significant impact on the U.S. economy and businesses. The social distancing and stay-at-home orders issued by national, state and local governments have resulted in closures of offices and factories and disrupted supply chains. The pandemic also has taxed healthcare systems both in the U.S. and around the world, resulting in disruption to or temporary suspension of clinical trials. The nature, extent and duration of the COVID-19 pandemic remains uncertain and the time needed for businesses and healthcare systems to recover remains unknown. The full impact of the pandemic on the economy, including the capital markets, also remains unknown. The continuation of prolonged adverse economic conditions (including due to any resurgence of COVID-19 infections) could limit the Company's access to financial resources from the capital markets and other sources. It is not possible to predict the full impact of the COVID-19 pandemic on the Company's business and access to capital in the future. Despite these challenges, the Company and its contract research organization, or CRO, partner were able to keep the ATTACK Phase 3 registration trial enrolling throughout the pandemic and announced positive top-line data in October 2021. Furthermore, the Company has observed an increase in the enrollment rate during the past two quarters in the zoliflodacin Phase 3 registration trial.

2. Summary of Significant Accounting Policies

Basis of Presentation and Consolidation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States, or U.S. GAAP. The consolidated financial statements include the Company's accounts and its wholly owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of the Company's consolidated financial statements in conformity with U.S. GAAP requires management to make estimates, judgments and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the reporting period. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the recognition of revenue and the recognition of research and development expenses. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ from the Company's estimates.

Fair Value Measurements

The accounting standard for fair value measurements defines fair value, establishes a framework for measuring fair value in accordance with U.S. GAAP, and requires detailed disclosures about fair value measurements. Under this standard, fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. The valuation techniques are based on observable and

unobservable inputs. Observable inputs reflect readily obtainable data from independent sources, while unobservable inputs reflect the Company's assumptions. This standard classifies these inputs into the following hierarchy:

Level 1 Inputs— Quoted prices in active markets for identical instruments;

Level 2 Inputs—Quoted prices for similar instruments in active markets; quoted prices for identical or similar instruments in markets that are not active; and model-derived valuations whose inputs are observable or whose significant value drivers are observable;

Level 3 Inputs—Instruments with primarily unobservable value drivers.

The Company evaluates transfers between levels at the end of each reporting period. There were no transfers of assets or liabilities between Level 1, Level 2 or Level 3 during the years ended December 31, 2021 and 2020.

Cash and Cash Equivalents

The Company considers all highly liquid investments purchased with original maturities of 90 days or less at acquisition to be cash equivalents. Cash and cash equivalents include cash held in banks, money market instruments, corporate and municipal notes, U.S. Treasury securities and federal agency securities. Cash equivalents are stated at fair value. The amount of cash equivalents included in cash and cash equivalents was approximately $28.1 million and $49.1 million as of December 31, 2021 and 2020, respectively.

Concentrations of Credit Risk and of Significant Suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and short-term investments. The Company maintains each of its cash balances with high-quality, accredited, financial institutions and, accordingly, such funds are not exposed to significant credit risk. The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

The Company is dependent on third-party manufacturers to supply active pharmaceutical ingredient, or API, and drug product for research and development activities for its programs, including clinical trial testing. These programs could be adversely affected by a significant interruption in the supply of API or drug product.

Deferred Financing Costs

The Company capitalizes certain legal, professional accounting and other third-party fees that are directly associated with in-process equity financings as deferred offering costs until such financings are consummated. After consummation of the equity financing, these costs are recorded in stockholders' equity as a reduction of proceeds generated as a result of the offering.

Should a planned equity financing be abandoned, the deferred offering costs would be expensed immediately as a charge to operating expenses in the consolidated statement of operations.

Property and Equipment

Property and equipment is recorded at cost and depreciated over the estimated useful lives of the related assets using the straight-line method. Upon disposal of an asset, the related cost and accumulated depreciation are removed from the asset accounts and any resulting gain or loss is included in the consolidated statement of operations. Repair and maintenance costs are expensed as incurred, whereas major improvements are capitalized as additions to property and equipment. The estimated useful lives of the Company's respective assets are as follows:

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

	Estimated Useful Life
Laboratory equipment	3 - 5 years
Computer software	3 years
Computer equipment	3 years
Furniture and fixtures	5 years

Impairment of Long-Lived Assets

Long-lived assets are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Whenever such events occur, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset over its fair value, determined based on discounted cash flows.

Segment Information

The Company manages its operations as a single operating segment for the purposes of assessing performance and making operating decisions. As of December 31, 2021 and 2020, all of the Company's long-lived assets were domiciled in the United States.

Revenue Recognition

The Company enters into collaboration agreements for research, development, manufacturing and commercial services, under which the Company licenses certain rights to its product candidates to third parties. The terms of these arrangements typically include payment to the Company of one or more of the following: non-refundable, upfront license fees; reimbursement of certain costs; customer option exercise fees; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products. The amount of variable consideration is constrained until it is probable that the revenue is not at a significant risk of reversal in a future period. The contracts into which the Company enters generally do not include significant financing components.

As part of the accounting for these arrangements, the Company may be required to use significant judgment to determine: (a) the performance obligations in the contract, (b) the transaction price and (c) the timing of revenue recognition, including the appropriate measure of progress. The Company uses judgment to determine whether milestones or other variable consideration, except for royalties, should be included in the transaction price, as described further below. The transaction price is allocated to each performance obligation on a relative stand-alone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied. If a milestone or other variable consideration relates specifically to the Company's efforts to satisfy a single performance obligation or to a specific outcome from satisfying the performance obligation, the Company generally allocates the milestone amount entirely to that performance obligation once it is probable that a significant revenue reversal would not occur.

Amounts received prior to revenue recognition are recorded as deferred revenue. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date would be classified as current portion of deferred revenue in the consolidated balance sheet. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date would be classified as deferred revenue, net of current portion.

Licenses of intellectual property

In assessing whether a license is distinct from the other promises, the Company considers factors such as the research, development, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the

collaboration partner can benefit from a license for its intended purpose without the receipt of the remaining promise(s), whether the value of the license is dependent on the unsatisfied promise(s), whether there are other vendors that could provide the remaining promise(s), and whether it is separately identifiable from the remaining promise(s). For licenses that are combined with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Customer options

If an arrangement is determined to contain customer options that allow the customer to acquire additional goods or services, the goods and services underlying the customer options are not considered to be performance obligations at the outset of the arrangement, as they are contingent upon option exercise. The Company evaluates the customer options for material rights, or options to acquire additional goods or services for free or at a discount. If the customer options are determined to represent or include a material right, the material right is recognized as a separate performance obligation at the outset of the arrangement. The Company allocates the transaction price to material rights based on the relative standalone selling price, which is determined based on the identified discount and the probability that the customer will exercise. Amounts allocated to a material right are not recognized as revenue until, at the earliest, the option is exercised.

Milestone payments

At the inception of each arrangement that includes development milestone payments, the Company evaluates whether the milestones are considered probable of being achieved and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant reversal of cumulative revenue would not occur, the associated milestone value is included in the transaction price. Milestone payments based on events that are not within the Company's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. The Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making this assessment. There is considerable judgment involved in determining whether it is probable that a significant reversal of cumulative revenue would not occur. At the end of each subsequent reporting period, the Company reevaluates the probability of achievement of all milestones subject to constraint and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenue and earnings in the period of adjustment.

Government Contracts and Grant Agreements

Income from grants is recognized in the period during which the related specified expenses are incurred, provided that the conditions under which the grants or incentives were provided have been met. Grant funding that is received by the Company in advance of incurring specified expenses is recorded in the consolidated balance sheet as a liability. Grant income recognized upon incurring specified expenses in advance of receipt of grant funding is recorded in the consolidated balance sheet as a receivable.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development expenses include employee costs, such as salaries, equity-based compensation and benefits, as well as consulting, contract research, third-party license fees, depreciation, rent and other corporate or operational costs attributable to the Company's research and development activities. These costs include allocated facility-related expenses and external costs of outside vendors engaged to conduct both preclinical studies and clinical trials. Non-refundable pre-payments for goods or services that will be used or rendered for future research and development activities are deferred. Such amounts are recognized as

expense as the goods or services are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered or the services rendered.

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. The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Patent Costs

The Company expenses patent costs as incurred and records such costs within general and administrative expenses.

Stock-Based Compensation

The Company measures stock-based awards based on the estimated fair value of the award on the date of the grant and recognizes compensation expense for those awarded to employees and directors over the requisite service period, which is generally the vesting period of the respective award, and for those awarded to nonemployees over the period during which services are rendered by nonemployees until completed. Forfeitures are accounted for as they occur. The Company has historically issued stock-based awards with only service-based vesting conditions and records the expense for these awards using the straight-line method.

The Company classifies stock-based compensation expense in its consolidated statement of operations in the same manner in which the award recipients' payroll costs are classified or in which the award recipients' service payments are classified.

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option pricing model. The Company lacks company-specific historical and implied volatility information for its stock. The Company estimates its expected stock price volatility based on the historical volatility of publicly traded peer companies and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded stock price. The expected term of the Company's stock options has been determined utilizing the "simplified" method. The "simplified" method estimates the expected term of stock options as the mid-point between the weighted average time to vesting and the contractual maturity. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. There is no expected dividend yield since the Company has never paid cash dividends on common stock and does not expect to pay any cash dividends in the foreseeable future.

Income Taxes

The Company accounts for income taxes using the asset and liability method which requires recognition of deferred tax assets and liabilities for the expected future tax consequences of temporary differences between the carrying amounts and the tax bases of assets and liabilities. Deferred tax assets and liabilities are determined based on the difference between the financial statement and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. A valuation allowance is provided to reduce the deferred tax asset to a level which, more likely than not, will be realized. See Note 11 for further discussion of income taxes.

Accounting for income taxes requires a two-step approach to recognize and measure uncertain tax positions. The first step is to evaluate the tax position for recognition by determining if, based on the technical merits, it is more likely than not that the position will be sustained upon audit, including resolution of related appeals or litigation

processes, if any. The second step is to measure the tax benefit as the largest amount that is more than 50 percent likely of being realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate as well as the related net interest and penalties.

Basic and Diluted Net Loss Per Share

Net earnings or loss per share is calculated in accordance with the applicable accounting guidance provided in ASC 260, *Earnings per Share.* The Company uses the two-class method for the computation and presentation of net income (loss) per common share. The two-class method is an earnings allocation formula that calculates basic and diluted net income (loss) per share for each class of common stock separately based on dividends declared and participation rights in undistributed earnings as if all such earnings had been distributed during the period. Under the two-class method, warrants issued to the investors in connection with the First Private Placement and the Second Private Placement are assumed to participate in undistributed earnings on an as-exercised basis, in accordance with the respective warrant agreements. Undistributed net losses are allocated entirely to common stockholders since the participating security has no contractual obligation to share in the losses.

Basic net income (loss) per share is computed by dividing the net income (loss) by the weighted average number of shares of common stock outstanding for the period. Diluted net income (loss) is computed by adjusting net income (loss) to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net income (loss) per share is computed by dividing the diluted net income (loss) by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of common stock equivalents.

Recently Adopted Accounting Pronouncements

Effective January 1, 2021, the Company adopted the provisions of FASB ASU 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes*, which simplifies the accounting for income taxes. The adoption of the new guidance did not affect the Company's consolidated financial statements.

Recently Issued Accounting Pronouncements

In November 2021, the FASB issued ASU 2021-10, *Government Assistance (Topic 832): Disclosures by Business Entities about Government Assistance*. This update requires annual disclosures about transactions with a government that are accounted for by applying a grant or contribution accounting model by analogy. This standard is effective for fiscal years beginning after December 15, 2021 and should be applied either prospectively or retrospectively. Early adoption is permitted. The Company is currently evaluating the impact of ASU 2021-10 on the consolidated financial statements.

3. Fair Value of Financial Instruments

The following tables set forth the Company's assets that were accounted for at fair value on a recurring basis:

	December 31, 2021			
	Fair Value Measurement Using			
	Level 1	Level 2	Level 3	Total
	(in thousands)			
Cash equivalents:				
Money market funds	$ 28,137	$ —	$ —	$ 28,137
Total	$ 28,137	$ —	$ —	$ 28,137

	December 31, 2020			
	Fair Value Measurement Using			
	Level 1	Level 2	Level 3	Total
	(in thousands)			
Cash equivalents:				
Money market funds	$ 49,125	$ —	$ —	$ 49,125
Total	$ 49,125	$ —	$ —	$ 49,125

The Company classifies its money market funds and U.S. Treasury securities as Level 1 assets under the fair value hierarchy as these assets have been valued using quoted market prices in active markets without any valuation adjustment.

The carrying amounts of the Company's cash equivalents, grants receivable, accounts payable and accrued expenses approximate their fair value due to the short-term nature of these amounts.

4. Property and Equipment, net

Property and equipment, net consisted of the following (in thousands):

	As of December 31,	
	2021	2020
Laboratory equipment	$ 1,039	$ 1,001
Computer software	87	71
Computer equipment	44	38
Furniture and fixtures	22	6
Total	1,192	1,116
Less: accumulated depreciation	(994)	(894)
Property and equipment, net	$ 198	$ 222

Depreciation expense was $0.1 million for each of the years ended December 31, 2021 and 2020.

5. Leases

The Company has one significant operating lease, consisting of 20,062 square feet of office and laboratory space in Waltham, Massachusetts that expires in December 2022 pursuant to a May 2015 lease with AstraZeneca, or the AZ lease, as amended in February 2018. During each of the years ended December 31, 2021 and December 31, 2020, the Company recorded lease expense of $0.6 million related to this lease. The Company has two additional operating leases that are included in its lease accounting which are not considered significant.

In calculating the present value of future lease payments, the Company utilized its incremental borrowing rate based on the remaining lease term at the date of adoption. The AZ lease contains a renewal option that can extend the lease for three years. As of December 31, 2021, the Company was not reasonably certain to exercise this renewal option. In February 2022, the Company made the decision to exercise this renewal option which will extend the lease term for an additional three years. Therefore, the option is not considered in determining the lease term, and associated potential additional payments are excluded from lease payments. The Company has elected to account for each lease component and its associated non-lease components as a single lease component and has allocated all of the contract consideration across lease components only. The Company has existing net leases in which the non-lease components (e.g., common area maintenance) are paid separately from rent based on actual costs incurred and therefore are not included in the operating lease right-of-use assets and lease liabilities and are reflected as an expense in the period incurred.

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

The following table summarizes the presentation of the Company's operating leases in its consolidated balance sheet (in thousands):

	As of December 31, 2021	2020
Assets		
Operating lease right-of-use assets	$ 604	$ 1,141
Liabilities		
Operating lease liabilities, current	$ 704	$ 617
Operating lease liabilities, net of current portion	—	704
Total operating lease liabilities	$ 704	$ 1,321

The operating lease right-of-use assets and operating lease liabilities balances relate primarily to amounts associated with the AZ lease. Future minimum lease payments under non-cancelable leases were as detailed below (in thousands):

Fiscal Year	As of December 31, 2021
2022	$ 737
2023	1
Total undiscounted lease payments	738
Less: imputed interest	(34)
Total operating lease liabilities	$ 704

As of December 31, 2021, the weighted-average remaining lease term was 1.0 years and the weighted-average incremental borrowing rate used to determine the operating lease right-of-use assets was 9.1%.

6. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following (in thousands):

	As of December 31, 2021	2020
Accrued compensation and benefits	$ 3,668	$ 2,935
Accrued contract manufacturing	2,678	2,959
Current portion of operating lease liabilities	704	617
Accrued clinical	691	504
Accrued professional services	375	435
Accrued research	292	349
Other	117	106
Total accrued expenses and other current liabilities	$ 8,525	$ 7,905

7. Funding Arrangements

NIH

In June 2020, the Company entered into a contract with the National Institute of Allergy and Infectious Diseases, or NIAID, part of the National Institutes of Health, or NIH, the NIH Contract, which was effective beginning July 1, 2020 and provides the Company with reimbursement of certain qualified expenses incurred. The initial award consisted of approximately $3.0 million, with the potential to increase up to $15.5 million, and will be used to develop

novel molecules from the Company's non-β-lactam inhibitor, or NBP, platform. Funding from the contract will support research towards developing molecules with expanded Gram-negative spectrum against antibiotic resistant bacterial pathogens including *E. coli*, *Acinetobacter*, *Pseudomonas* and *Klebsiella*. In July 2021, the Company successfully completed the first milestones for the program associated with the initial award and has been awarded the Option 1 Period of the program to proceed with further optimization, beginning August 1, 2021. This option consists of an additional $2.9 million, bringing the total award to $5.9 million. Through December 31, 2021, the Company has received $3.2 million in payments and recorded $3.9 million of grant income under this contract.

The Company recognized grant income in connection with the NIH contract of $2.6 million during the year ended December 31, 2021 and $1.3 million during the year ended December 31, 2020. As of December 31, 2021, and December 31, 2020 the Company's receivables for unreimbursed, eligible costs incurred under the NIH contract totaled $0.6 million, including both billed and unbilled amounts.

CARB-X

In March 2017 and October 2017, the Company entered into funding arrangements with the Trustees of Boston University to utilize funds from the U.S. government through the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, program, in support of the Company's ETX0282CPDP and ETX0462 programs. The amount of specified research expenditures of the Company that could be covered is $18.5 million from April 2017 through May 2023. Through December 31, 2021, the Company had received $12.6 million in payments and recorded $12.9 million of grant income under these funding arrangements. The remaining $5.6 million that could be received is related to the Company's ETX0462 program.

The Company recognized grant income in connection with the CARB-X agreements of $2.6 million during the year ended December 31, 2021, and $2.3 million during the year ended December 31, 2020. As of December 31, 2021 and 2020, the Company's receivables for unreimbursed, eligible costs incurred under the CARB-X agreements totaled $0.7 million and $1.1 million, respectively, including both billed and unbilled amounts.

8. License and Collaboration Agreements

GARDP

In July 2017, the Company entered into a collaboration agreement with the Global Antibiotic Research and Development Partnership, or GARDP, for the development, manufacture and commercialization of the product candidate zoliflodacin in certain countries. Under the terms of the collaboration agreement, GARDP will use commercially reasonable endeavors to perform and fully fund the Phase 3 registration trial, including the manufacture and supply of the product candidate containing zoliflodacin, in uncomplicated gonorrhea. The Phase 3 registration trial was initiated in September 2019 with activation of U.S. sites. The trial was negatively impacted by the COVID-19 pandemic, resulting in a 4-month pause in enrollment in mid-2020. Although GARDP resumed patient enrollment into the Phase 3 registration trial after the pause, any future impact by the continued COVID-19 pandemic at clinical trial sites cannot be estimated at this time. The Company has observed an increase in the enrollment rate during the past two quarters and now anticipates the Phase 3 trial to be fully enrolled in 2023.

In addition, under the collaboration agreement, the Company has granted GARDP a worldwide, fully paid, exclusive and royalty-free license, with the right to sublicense, to use its zoliflodacin technology in connection with GARDP's development, manufacture and commercialization of zoliflodacin in low-income and specified middle-income countries. The Company has retained commercial rights in all other countries worldwide, including the major markets in North America, Europe and Asia-Pacific. The Company has also retained the right to use and grant licenses to its zoliflodacin technology to perform its obligations under the collaboration agreement and for any purpose other than gonorrhea or community-acquired indications. If the Company believes that the results of the Phase 3 registration trial of zoliflodacin would be supportive of an application for marketing approval, it is obligated to use its best efforts to file an application for marketing approval with the FDA within six months of the completion of the trial and to use commercially reasonable endeavors to file an application for marketing approval with the EMA. Each party is

responsible for using commercially reasonable efforts to obtain marketing authorizations for the product candidate in their respective territories.

Zai Lab

In April 2018, the Company entered into a license and collaboration agreement with Zai Lab (Shanghai) Co., Ltd., or Zai Lab, pursuant to which Zai Lab licensed exclusive rights to durlobactam and sulbactam-durlobactam, or SUL-DUR, in the Asia-Pacific region, or the Zai Agreement. Under the terms of the Zai Agreement, Zai Lab will fund most of the Company's clinical trial costs in China for SUL-DUR, including all costs in China for the Company's Phase 3 registration trial of SUL-DUR, with the exception of Phase 3 patient drug supply. Zai Lab will conduct development activities and plan and obtain regulatory approval in a specified number of countries in the Asia-Pacific region beyond China after receipt of regulatory approval of a licensed product in China. Zai Lab is also solely responsible for commercializing licensed products in the Asia-Pacific region and will commercialize licensed products for which it has obtained regulatory approval. The Company is obligated to supply Zai Lab with the licensed products for clinical development, although Zai Lab may take over manufacturing responsibilities for its own commercialization activities within a specified time period following the effective date of the Zai Agreement.

The Company received an upfront, non-refundable payment of $5.0 million, milestone payments of $7.0 million, research support funding of $0.6 million and certain other reimbursable registration trial costs of $5.4 million, less applicable taxes of $2.2 million, from Zai Lab through December 31, 2021. During the years ended December, 2021 and 2020, the Company recognized no revenue under the Zai Agreement. The Company is eligible to receive up to an aggregate of $91.0 million in additional research and development support payments and development, regulatory and sales milestone payments related to SUL-DUR, imipenem and other combinations with the licensed products. Zai Lab will pay the Company a tiered royalty ranging from a high-single digit to low-double digit percentage based on annual net sales of licensed products in the territory, subject to specified reductions for the market entry of competing products, loss of patent coverage of licensed products and for payments owed to third parties for additional rights necessary to commercialize licensed products in the territory. Payments received for research support and reimbursable clinical trial costs are recorded as an offset to research and development expense during the period in which the qualifying expenses are incurred.

Future potential milestone payments were excluded from the initial transaction price as they were fully constrained as the risk of significant reversal of revenue had not yet been resolved. At the outset of the Zai Agreement, the achievement of the future potential milestones was not within the Company's control and was subject to certain research and development success, regulatory approvals or commercial success and therefore carried significant uncertainty. The Company reevaluates the likelihood of achieving the future milestones at the end of each reporting period. Future development milestone revenue from the arrangement will be recognized as revenue in the period when it is no longer probable that revenue attributable to the milestone will result in a significant reversal of cumulative revenue.

9. Stockholders' Equity

Common Stock

Each holder of common stock shall be entitled to one vote for each share of common stock held of record by such holder on all matters on which stockholders generally are entitled to vote. Common stockholders are entitled to receive dividends when and if declared by the board of directors, out of any funds legally available. As of December 31, 2021, no dividends have been declared or paid.

Third Private Placement

On May 3, 2021, the Company entered into the Third Securities Purchase Agreement, with a subsidiary of Innoviva, pursuant to which the Company agreed to issue and sell to Innoviva up to 10,000,000 newly issued shares of common stock of the Company at $2.00 per share and warrants to purchase up to 10,000,000 shares of common stock, each with an exercise price per share of $2.00.

Third Private Placement occurred in two tranches. At the First Closing, which occurred on May 3, 2021, Innoviva purchased 3,731,025 shares of common stock and warrants to purchase 3,731,025 shares of common stock, for aggregate gross proceeds of $7.5 million. At the Second Closing, which occurred on June 11, 2021, Innoviva purchased the remaining 6,268,975 shares of common stock and warrants to purchase 6,268,975 shares of common stock, for aggregate gross proceeds of $12.5 million.

Second Private Placement

On August 27, 2020, the Company entered into the Second Securities Purchase Agreement with the Investors, including existing stockholder Innoviva, pursuant to which the Company issued and sold to the Investors in a private placement (i) 8,183,878 newly issued shares of common stock of the Company at $2.675 per share, (ii) warrants to purchase an aggregate of 9,345,794 shares of common stock with and exercise price of $2.675, and (iii) pre-funded warrants, in lieu of common stock, to purchase an aggregate of 1,161,916 shares of common stock, with an exercise price of $0.001 per share, resulting in aggregate gross proceeds of approximately $25.0 million. The closing of the Second Private Placement occurred on September 1, 2020.

The exercise price and the number of shares of common stock issuable upon exercise of each warrant is subject to appropriate adjustments in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting the Company's common stock. Each warrant is exercisable from the date of issuance and has a term of five years.

First Private Placement

On April 12, 2020, the Company entered into the First Securities Purchase Agreement, with Innoviva, pursuant to which the Company issued and sold to Innoviva 14,000,000 newly issued shares of common stock of the Company at $2.50 per share, and warrants to purchase up to 14,000,000 shares of common stock with an exercise price per share of $2.50.

Under the First Securities Purchase Agreement, the First Private Placement occurred in two tranches. At the closing of the first tranche, which occurred on April 22, 2020, or the First Closing, Innoviva purchased 1,322,510 shares of common stock and warrants to purchase 1,322,510 shares of common stock, for an aggregate gross purchase price of approximately $3.3 million. At the closing of the second tranche, which occurred on June 11, 2020, or the Second Closing, Innoviva purchased the remaining 12,677,490 shares of common stock and warrants to purchase 12,677,490 shares of the common stock for an aggregate gross purchase price of approximately $31.7 million.

As of December 31, 2021, Innoviva owned approximately 59.9% of the Company's outstanding common stock without giving effect to the potential exercise of the warrants.

At-the-Market Facility

In August 2021, the Company entered into a Controlled Equity Offering Sales Agreement, or Sales Agreement, with Cantor Fitzgerald & Co, or Cantor, for the offer and sale of up to $17.5 million of its common stock at the then current market prices in amounts to be determined from time to time. On October 21, 2021, the Company sold an aggregate of 200,000 shares of common stock at a sale price of $3.25 per share, for gross proceeds of $0.7 million. Proceeds, net of fees, were $0.6 million.

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

Warrants

As of December 31, 2021, outstanding warrants to purchase shares of the Company's common stock are as follows:

Shares Underlying Outstanding Warrants	Exercise Price	Expiration Date
1,322,510	$ 2.50	April 22, 2025
12,677,490	$ 2.50	June 11, 2025
8,672,897	$ 2.675	September 1, 2025
10,000,000	$ 2.00	May 3, 2026
32,672,897		

10. Stock-Based Compensation Expense

Stock Incentive Plan

In September 2018, the Company's board of directors adopted and its stockholders approved the 2018 Equity Incentive Plan, or the 2018 Plan, which became effective on September 25, 2018, at which point no further grants will be made under the 2015 Stock Incentive Plan, or the 2015 Plan, previously in effect. Under the 2018 Plan, the Company may grant incentive stock options, or ISOs, non-statutory stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards. As of December 31, 2021, options to purchase an aggregate of 5,213,285 shares had been granted, restricted stock units, or RSUs, of 992,600 had been awarded, and 1,604,834 shares were available for future issuance under the 2018 Plan. The options issued under the 2018 Plan expire after 10 years from the date of grant.

At its inception, the aggregate number of shares of the Company's common stock available for issuance under the 2018 Plan was 2,350,000. The number of shares of the Company's common stock reserved for issuance under the 2018 Plan will automatically increase on January 1 of each year, for a period of 10 years, from January 1, 2019 continuing through January 1, 2028, by 4% of the total number of shares of the Company's common stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares as may be determined by the Company's board of directors. Accordingly, on January 1, 2022 and 2021, 1,914,071 and 1,465,494 shares were added to the number of available shares, respectively. The maximum number of shares that may be issued pursuant to the exercise of ISOs under the 2018 Plan is 7,500,000.

The maximum number of shares of the Company's common stock subject to awards granted under the 2018 Plan or otherwise during a single calendar year to any nonemployee directors, taken together with any cash fees paid by the Company to such nonemployee directors during the calendar year for serving on the Company's board of directors, will not exceed $500,000 in total value, or, with respect to the calendar year in which a nonemployee director is first appointed or elected to the Company's board of directors, $800,000.

All options and awards granted under the 2015 Plan consisted of the Company's common stock. As of September 25, 2018, no additional stock awards have been or will be granted under the 2015 Plan. Although the 2015 Plan was terminated as to future awards in September 2018, it continues to govern the terms of options that remain outstanding under the 2015 Plan.

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

Stock Option Activity

Stock option activity under both plans for year ended December 31, 2021 is summarized as follows:

	Number of Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2020	3,112,704	$ 5.58	7.76	$ 44
Granted	1,492,776	2.45		
Forfeited and expired	(1,710,100)	6.86		
Outstanding as of December 31, 2021	2,895,380	$ 3.21	8.33	$ 30
Exercisable as of December 31, 2021	978,915	$ 3.84	6.57	$ 7

The aggregate intrinsic value of options is calculated as the difference between the exercise price of the options and the fair value of the Company's common stock for those options that had exercise prices lower than the fair value of the Company's common stock.

During the years ended December 31, 2021 and 2020 the weighted-average grant-date fair value per granted option was $4.03 and $2.95, respectively.

As described below, on July 16, 2021, the Company completed a stock option exchange program that resulted in the termination of options to purchase 1,562,752 shares of the Company's common stock with a weighted-average exercise price of $7.17 per share and the issuance of stock options to purchase 1,148,572 shares of the Company's common stock with an exercise price of $2.44 per share.

Stock Option Exchange

On June 17, 2021, the Company commenced a voluntary stock option exchange program, or the Exchange Program, to permit the Company's eligible employees, directors and certain consultants to exchange some or all of their eligible outstanding options, or the Original Options, to purchase the Company's common stock with an exercise price greater than or equal to $4.98 per share, whether vested or unvested, for a lesser number of new stock options, or the New Options. The New Options will be granted under the 2018 Plan on the date on which the Original Options accepted for exchange are cancelled. Participants must remain continuously employed by the Company or in continuous service to the Company through the New Option grant date. New Options will have a per share exercise price equal to the per share closing price of the Company's common stock on the New Option grant date. The New Options will have the same vesting schedule as the Original Options for options with a remaining vesting period exceeding 12 months. For Original Options with a remaining vesting period of 12 months or less, including full vesting options, the replacement options will vest in full 12 months from the New Option grant date. In accordance with the terms and conditions of the Exchange Program, the Company closed the exchange program and accepted all exchanged outstanding options on July 16, 2021, at which time the Company's common stock price per share was $2.44. The stock option exchange program was approved at the Company's annual shareholder meeting on June 10, 2021.

Pursuant to the Exchange Program, 44 eligible participants elected to exchange, and the Company accepted for cancellation Original Options to purchase an aggregate of 1,562,752 shares of the Company's common stock, representing approximately 97% of the total shares of common stock underlying the eligible Original Options. On July 16, 2021, immediately following the expiration of the exchange offer, the Company granted New Options to purchase 1,148,572 shares of common stock, pursuant to the terms of the exchange offer and the Company's 2018 Plan. In addition to the grant date fair value of the original awards, the Company will recognize incremental expense of approximately $0.3 million over the remaining service periods of the replacement awards.

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

Restricted Stock Unit Activity

Restricted stock unit activity for the year ended December 31, 2021 is summarized as follows:

	Number of Units	Weighted-Average Grant Date Fair Value
Outstanding as of December 31, 2020	395,100	$ 1.65
Granted	597,500	2.57
Released	(427,975)	2.24
Forfeited	(73,650)	1.99
Outstanding as of December 31, 2021	490,975	$ 2.20

Employee Stock Purchase Plan

In September 2018, the Company's board of directors and its stockholders approved the 2018 Employee Stock Purchase Plan, or the ESPP, which became effective as of September 25, 2018. The ESPP is intended to qualify as an "employee stock purchase plan" within the meaning of Section 423 of the U.S. Internal Revenue Code of 1986, as amended. The number of shares of common stock initially reserved for issuance under the ESPP was 140,000 shares. The ESPP provides for an annual increase on the first day of each year beginning in 2019 and ending in 2028, in each case subject to the approval of the board of directors, equal to the lesser of (i) 1% of the shares of common stock outstanding on the last day of the prior fiscal year or (ii) 250,000 shares; provided, that prior to the date of any such increase, the board of directors may determine that such increase will be less than the amount set forth in clauses (i) and (ii). Pursuant to the terms of the 2018 Employee Stock Purchase Plan, an additional 250,000 shares were added to the number of available shares effective January 1, 2022 and 2021. As of December 31, 2021, no shares of common stock had been issued under the ESPP and 654,163 shares remained available for future issuance under the ESPP. No offering period under the ESPP has been set by the Company's board of directors.

Stock-Based Compensation

Stock-based compensation expense was classified in the consolidated statement of operations as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Research and development	$ 1,932	$ 1,397
General and administrative	2,091	1,554
Total stock-based compensation expense	$ 4,023	$ 2,951

The following table summarizes stock-based compensation expense by type of award (in thousands):

	Year Ended December 31,	
	2021	2020
Stock options	$ 2,714	$ 2,898
Restricted stock units	1,309	53
Total stock-based compensation expense	$ 4,023	$ 2,951

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

The following table summarizes unrecognized stock-based compensation expense as of December 31, 2021, by type of awards, and the weighted-average period over which that expense is expected to be recognized. The total unrecognized stock-based compensation expense will be adjusted for actual forfeitures as they occur.

	As of December 31, 2021	
	Unrecognized Expense (in thousands)	Weighted-average Remaining Recognition Period (in years)
Stock options	$ 1,945	1.69
Restricted stock units	$ 679	0.72

The following weighted average assumptions were used to calculate the fair value of each stock option award under the Black-Scholes option pricing model:

	Year Ended December 31,	
	2021	2020
Expected stock price volatility	80.7 %	82.0 %
Risk-free interest rate	0.9 %	0.5 %
Expected annual dividend yield	—	—
Expected life of options	6.1 years	6.3 years

11. Income Taxes

During the years ended December 31, 2021 and 2020, the Company recorded no income tax benefits for the net operating losses incurred due to its uncertainty of realizing a benefit from those items. The Company's losses before income taxes were generated in the United States and the United Kingdom.

Net loss before the provision for income taxes for the years ended December 31, 2021 and 2020, consisted of the following (in thousands):

	Year Ended December 31,	
	2021	2020
United Kingdom	$ 28,411	$ 38,280
United States	18,730	12,216
	$ 47,141	$ 50,496

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

A reconciliation of the federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31,	
	2021	2020
Income tax benefit computed at U.S. statutory tax rate	21.0 %	21.0 %
State taxes, net of federal benefit	6.4	6.6
Foreign rate differential	(1.2)	(1.5)
Disregarded entity	12.7	15.9
Research and development tax credits	1.4	1.4
Permanent difference	(1.2)	(0.6)
Valuation allowances	(58.9)	(45.7)
Rate change	20.0	3.6
Other	(0.2)	(0.7)
Effective income tax rate	(0.0)%	(0.0)%

Net deferred tax assets consisted of the following (in thousands):

	As of December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 84,786	$ 57,265
Tax credit carryforwards	5,261	4,345
Accrued expenses and other	2,275	3,099
Total deferred tax assets	92,322	64,709
Deferred tax liabilities:		
Right-of-use asset	(165)	(312)
Total deferred tax liabilities	(165)	(312)
Valuation allowance	(92,157)	(64,397)
Net deferred tax assets	$ —	$ —

Net operating losses generated in years ending after December 31, 2018 will be carried forward indefinitely and can no longer be carried back, and net operating losses generated in years beginning after December 31, 2017, can only reduce taxable income by 80% when utilized in a future period. As of December 31, 2021, the Company had federal and state net operating loss carryforwards, or NOLs, of $166.3 million and $167.4 million, respectively, which begin to expire in 2035. Included in the $166.3 million of federal net operating losses are losses of $153.6 million that will carry forward indefinitely as a result of the Tax Cuts and Jobs Act. As of December 31, 2021, the Company had federal and state research and development tax credits carryforwards of $4.1 million and $1.4 million, respectively, which begin to expire in 2035 and 2026, respectively.

Utilization of the NOLs and research and development tax credit carryforwards may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986 due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 50% over a three-year period. During 2020, Innoviva purchased over 50% of the Company's common stock. This ownership change may result in a limitation of the Company's NOLs. The Company has not conducted a study to assess whether there have been multiple changes of control since inception due to the significant complexity and cost associated with such a study. Ownership changes may limit the amount of NOLs and tax credit carryforwards that could be utilized annually to offset future taxable income. The amount of the annual limitation is determined based on the Company's value immediately prior to the ownership change. Subsequent significant changes in ownership could affect

the limitations in future years. Any limitation may result in expiration of a portion of the net operating loss carryforwards or tax credit carryforwards before utilization.

As of December 31, 2021, the Company had NOLs in the United Kingdom of $157.2 million to offset future taxable income. The NOLs in the United Kingdom can be carried forward indefinitely.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets. Management has considered the Company's history of cumulative net losses incurred since inception and its lack of commercialization of any products or generation of any revenue from product sales since inception and has concluded that it is more likely than not that the Company will not realize the benefits of the federal, state and foreign deferred tax assets. Accordingly, a full valuation allowance of $92.2 million has been established against the deferred tax assets as of December 31, 2021. Management reevaluates the positive and negative evidence at each reporting period.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2021 and 2020 related primarily to the increases in NOLs and research and development tax credit carryforwards and were as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Valuation allowance at beginning of year	$ (64,397)	$ (41,253)
Increases recorded to income tax provision	(27,760)	(23,144)
Valuation allowance at end of year	$ (92,157)	$ (64,397)

The Company has not recorded an amount for unrecognized tax benefits or related interest and penalties accrued as of December 31, 2021. The Company files income tax returns in the United States, Massachusetts and the United Kingdom. The federal and state returns are generally subject to tax examinations for the tax years ended December 31, 2015 to the present. The statute of limitations for assessment by the United Kingdom is open for the tax years since 2015. There are currently no pending tax examinations. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service and state tax authorities to the extent utilized in a future or prior period. The Company's policy is to record interest and penalties related to income taxes as part of its income tax provision.

12. Net Loss per Share

Basic and diluted net loss per share of the Company was calculated as follows (in thousands, except share and per share amounts):

	Year Ended December 31,	
	2021	2020
Numerator:		
Net loss	$ (47,141)	$ (50,496)
Net loss attributable to common stockholders—basic and diluted	$ (47,141)	$ (50,496)
Denominator:		
Weighted average common stock outstanding—basic and diluted	43,340,826	24,060,615
Net loss per share attributable to common stockholders—basic and diluted	$ (1.09)	$ (2.10)

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

The following outstanding securities have been excluded from the computation of diluted weighted average shares outstanding for the year ended December 31, 2021 and 2020, respectively, as they would have been anti-dilutive:

	As of December 31,	
	2021	2020
Options to purchase shares of common stock	2,895,380	3,112,704
Warrants to purchase shares of common stock	32,672,897	23,345,794
Unvested restricted stock units	490,975	395,100
	36,059,252	26,853,598

13. Commitments

Lease Commitments

The Company has an operating lease agreement for its office and laboratory space with AstraZeneca. See Note 5, *Leases*, for additional information.

AstraZeneca Subscription Agreement

In connection with the Company's spin-out from AstraZeneca in 2015, the Company entered into a business transfer and subscription agreement with AstraZeneca, or the AstraZeneca Subscription Agreement, pursuant to which the Company agreed to pay AstraZeneca a one-time milestone payment of $5.0 million within three months of achieving a specified cumulative net sales milestone for durlobactam. This milestone payment will be automatically waived should the Company's common stock trade on Nasdaq at or above a specified price at the time it achieves such specified cumulative net sales milestone for durlobactam. The Company is also obligated to pay AstraZeneca a one-time milestone payment of $10.0 million within two years of achieving the first commercial sale of zoliflodacin. At the Company's election, either milestone payment may be paid in cash, common stock, or a combination of cash and common stock. Additionally, the Company is obligated to pay AstraZeneca tiered, single-digit, per-country royalties on the annual worldwide net sales of durlobactam and zoliflodacin.

14. Related Party Transactions

AstraZeneca

The Company was formed in May 2015 as a wholly owned subsidiary of AstraZeneca. Prior to the closing of the initial public offering on September 28, 2018, AstraZeneca was the sole holder of Series A preferred stock. Upon the closing of the initial public offering, all shares of preferred stock converted into shares of common stock. AstraZeneca continues to maintain an ownership interest in the Company. The Company has an operating lease agreement for its office and laboratory space with AstraZeneca. See Note 5, *Leases*, for additional information.

Pharmaron Beijing Co., Ltd. (China)

The Company contracts with Pharmaron Beijing Co., Ltd. (China), or Pharmaron, to provide various medicinal chemistry research, manufacturing development and clinical services related to the Company's ongoing product candidates. The Company began utilizing Pharmaron as a service provider prior to the spin-out in 2015, and this relationship has continued through 2020. In 2019, the Senior Vice President of Strategic Partnerships at Pharmaron began sharing a household with the Company's Chief Executive Officer and, as a result, the Company considers the agreements between the Company and Pharmaron to be related-party transactions. The Company recorded expense of $3.7 million and $5.0 million during the years ended December 31, 2021 and December 31, 2020, respectively, for services pursuant to multiple Pharmaron agreements. Amounts due to Pharmaron were $0.1 million and $2.0 million as of December 31, 2021 and December 31, 2020, respectively.

ENTASIS THERAPEUTICS HOLDINGS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (CONTINUED)

15. Benefit Plans

The Company has a tax-qualified employee savings and retirement 401(k) plan, covering all qualified employees. Participants may elect a salary deferral up to the statutorily prescribed annual limit for tax-deferred contributions. The Company made matching contributions of $0.3 million for the years ended December 31, 2021 and 2020.

16. Subsequent Events

Securities Purchase Agreement

On February 17, 2022, the Company entered into a securities purchase agreement, or Fourth Securities Purchase Agreement with a subsidiary of Innoviva, pursuant to which the Company issued and sold to Innoviva, in a private placement which closed on February 18, 2022, a convertible promissory note having a principal amount of $15.0 million, or the Convertible Note. The Convertible Note is convertible at maturity at the election of the Company or Innoviva into shares of the Company's common stock at a conversion price of $1.48 per share of common stock and warrants to purchase an equal number of shares of common stock with an exercise price of $1.48 per share of common stock, or the Warrants. The Convertible Note will also be convertible at the option of Innoviva if the Company engages in certain capital markets transactions, asset sales or royalty transactions. If the Company is acquired prior to the maturity date of the Convertible Note, the Convertible Note will be payable in cash at the time of such acquisition. The Convertible Note will mature on August 18, 2022 and bears interest at a rate of 0.59% per annum to, but excluding, the date of repayment or conversion of the Convertible Note. From and including the date of maturity, if not converted, the Convertible Note will bear interest at a rate of 10.00% per annum to, but excluding, the date of repayment or conversion of the Convertible Note.

The Convertible Note and the Warrants will have provisions that preclude conversion or exercise, respectively, if such conversion or exercise would result in the issuance of more than 19.99% of the Company's currently outstanding common stock in the aggregate prior to obtaining stockholder approval.

Registration Rights Agreement

On February 18, 2022, the Company and Innoviva entered into a registration rights agreement, or the Registration Rights Agreement, pursuant to which, among other things, the Company must prepare and file with the Securities and Exchange Commission, or the SEC, a registration statement with respect to the resale of shares of common stock and the warrants issuable upon conversion of the Convertible Note and shares of common stock issuable upon exercise of the Warrants.

AZ Lease

In February 2022 the Company made the decision to exercise the renewal option within the AZ lease which will extend the lease term for an additional three years.

Exhibit 21.1

SUBSIDIARIES OF ENTASIS THERAPEUTICS HOLDINGS INC.

Name	Jurisdiction of Incorporation
Entasis Therapeutics Inc.	Delaware
Entasis Therapeutics Limited	United Kingdom
Entasis Therapeutics Security Corporation	Massachusetts
Entasis Therapeutics (Ireland) Limited	Ireland

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the registration statements (No. 333-228384, 333-230593, 333-238076 and 333-2411672) on Form S-8 and (No. 333-234041, 333-241683 and 333-249315) on Form S-3 of our report dated March 3, 2022, with respect to the consolidated financial statements of Entasis Therapeutics Holdings Inc.

/s/ KPMG LLP

Boston, Massachusetts
March 3, 2022

ENTASIS THERAPEUTICS HOLDINGS INC.

SECOND AMENDED NON-EMPLOYEE DIRECTOR COMPENSATION POLICY

Each member of the Board of Directors (the "***Board***") of Entasis Therapeutics Holdings Inc. (the "***Company***") who is not also serving as an employee of the Company or any of its subsidiaries (each such member, an "***Eligible Director***") will receive the compensation described in this Non-Employee Director Compensation Policy (this "***Policy***"). An Eligible Director may decline all or any portion of his or her compensation by giving notice to the Company prior to the date cash is to be paid or equity awards are to be granted, as the case may be. This Policy may be amended at any time in the sole discretion of the Board or the Compensation Committee of the Board.

Annual Cash Compensation

The annual cash compensation amount set forth below is payable to Eligible Directors in equal quarterly installments, payable in arrears on the last day of each fiscal quarter in which the service occurred. If an Eligible Director joins the Board or a committee of the Board at a time other than effective as of the first day of a fiscal quarter, each annual retainer set forth below will be pro-rated based on days served in the applicable fiscal year, with the pro-rated amount paid for the first fiscal quarter in which the Eligible Director provides the service, and regular full quarterly payments to be paid thereafter. All annual cash fees are vested upon payment.

1. Annual Board Service Retainer:
   a. All Eligible Directors: $40,000
   b. Non-executive chairperson of the Board: $90,000 (inclusive of Annual Board Service Retainer)

2. Annual Committee Member Service Retainer:
   a. Member of the Audit Committee: $9,000
   b. Member of the Compensation Committee: $7,500
   c. Member of the Nominating and Corporate Governance Committee: $4,500

3. Annual Committee Chair Service Retainer (inclusive of Committee Member Service Retainer):
   a. Chairperson of the Audit Committee: $18,000
   b. Chairperson of the Compensation Committee: $15,000
   c. Chairperson of the Nominating and Corporate Governance Committee: $8,500

The Company will also reimburse each of the Eligible Directors for his or her travel expenses incurred in connection with his or her attendance at Board and committee meetings. Such reimbursements shall be paid on the same date as the annual cash fees are paid.

Equity Compensation

The equity compensation set forth below will be granted under the Company's 2018 Equity Incentive Plan (the "***Plan***"), subject to the approval of the Plan by the Company's stockholders. All stock options granted under this Policy will be nonstatutory stock options, with an exercise price per share equal to 100% of the Fair Market Value (as defined in the Plan) of the underlying common stock on the date of

grant, and a term of 10 years from the date of grant (subject to earlier termination in connection with a termination of service as provided in the Plan).

1. Initial Grant: For each Eligible Director who is first elected or appointed to the Board following the effective date of this Policy, on the date of such Eligible Director's initial election or appointment to the Board (or, if such date is not a market trading day, the first market trading day thereafter), the Eligible Director will be automatically, and without further action by the Board or Compensation Committee of the Board, granted a stock option to purchase a number of shares of the Company's common stock equal to 22,000 shares of the Company's common stock. The shares subject to each such stock option will vest monthly over a three-year period, subject to the Eligible Director's Continuous Service (as defined in the Plan) on each vesting date.

2. Annual Grant: On the date of each annual stockholder meeting of the Company held after the Effective Date, each Eligible Director who continues to serve as a non-employee member of the Board following such stockholder meeting will be automatically, and without further action by the Board or Compensation Committee of the Board, granted a stock option to purchase 11,000 shares of the Company's common stock (the "***Annual Grant***"). The shares subject to the Annual Grant will vest in equal monthly installments over the 12 months following the date of grant, provided that the Annual Grant will in any case be fully vested on the date of Company's next annual stockholder meeting, subject to the Eligible Director's Continuous Service (as defined in the Plan) through such vesting date and will vest in full upon a Change in Control (as defined in the Plan).

Approved: December 15, 2021
Effective: January 1, 2022

Amendment to Incentive Stock Option Agreement (Employees)
Issued under Amended and Restated Stock Incentive Plan

This Amendment to Nonqualified Stock Option Agreement (Employees) ("Amendment") issued under the Amended and Restated Stock Incentive Plan (the "Plan") of Entasis Therapeutics Holdings Inc. (the "Company") is made effective as of November 10, 2021 ("Effective Date") and modifies the outstanding Incentive Stock Options Agreement(s) (Senior Management) ("Option Agreements") existing as of the Effective Date between the Company and Optionee. Capitalized terms not explicitly defined in this Amendment or the Option Agreement(s), shall have the meanings set forth in the Plan.

Except as expressly modified by this Amendment, all of the terms of the Option Agreement(s) and the Plan shall remain in full force and effect.

The following provision is added as paragraph 14 to the Option Agreement(s):

14. Acceleration upon a Change in Control Termination. If after a Change in Control, some or all of Optionee's Options remain outstanding (for example, because they were substituted or assumed by the surviving or acquiring corporation), the portion of any Option that is unvested shall fully vest and become immediately exercisable in the event of a Change in Control Termination (as defined below). This right to accelerated vesting shall in no way (i) limit the Board's discretion to take the actions set forth in Section 10 of the Plan in the event of a Transaction, (ii) alter other terms of the Option Agreement(s), including extending the maximum term of the Award, or (iii) apply to any awards granted after the Effective Date, unless such future awards provide for such accelerated vesting.

As used herein, "Change in Control Termination" means termination of Optionee's service to the Company (or any surviving or acquiring corporation or entity) without Cause or Optionee's resignation for Good Reason (as defined below), in each case, only if such termination of service occurs during the period beginning on the date of the Change in Control and ending on the twelve-month anniversary of the Change in Control.

As used herein, "Good Reason" means any of the following actions taken by the Company (or any surviving or acquiring corporation or entity) without Optionee's consent: (i) any material diminution of Optionee's authority, duties or responsibilities; (ii) a material (greater than ten percent (10%)) reduction by the Company (or any surviving or acquiring corporation or entity) of Optionee's Base Salary except in the case of across-the-board salary reductions similarly affecting all or substantially all similarly-situated employees of the Company or any surviving or acquiring corporation or entity; (iii) a relocation of Optionee's place of employment to a location in excess of fifty (50) miles from the Company's last known principal place of employment; *provided*, *however*, with respect to each clause (i) through (iii), above, it will only be deemed Good Reason if (1) prior to Optionee's resignation, the Company (or any surviving or acquiring corporation or entity) has not previously notified the Optionee of its intention to terminate his/her employment; (2) the Company (or any surviving or acquiring corporation or

entity) is given written notice from Optionee within ninety (90) days following the first occurrence of a condition that Optionee considers to constitute Good Reason (with such notice including a description of the condition); (3) the Company (or any surviving or acquiring corporation or entity) fails to remedy such condition within thirty (30) days following such written notice, and (4) Optionee resigns from employment effective not later than fourteen (14) days after the end of the cure period. Notwithstanding the foregoing, any actions taken to accommodate a disability of Optionee or pursuant to the Family and Medical Leave Act or an applicable state leave law will not be a Good Reason for purposes of this Agreement.

This Amendment shall be deemed part of the Option Agreement(s) as of the Effective Date.

Amendment to Incentive Stock Option Agreement (Senior Management)
Issued under Amended and Restated Stock Incentive Plan

This Amendment to Nonqualified Stock Option Agreement (Senior Management) ("Amendment") issued under the Amended and Restated Stock Incentive Plan (the "Plan") of Entasis Therapeutics Holdings Inc. (the "Company") is made effective as of November 10, 2021 ("Effective Date") and modifies the outstanding Incentive Stock Options Agreement(s) (Senior Management) ("Option Agreements") existing as of the Effective Date between the Company and Optionee. Capitalized terms not explicitly defined in this Amendment or the Option Agreement(s), shall have the meanings set forth in the Plan.

Except as expressly modified by this Amendment, all of the terms of the Option Agreement(s) and the Plan shall remain in full force and effect.

The following provision is added as paragraph 15 to the Option Agreement(s):

15. Acceleration upon a Change in Control Termination. If after a Change in Control, some or all of Optionee's Options remain outstanding (for example, because they were substituted or assumed by the surviving or acquiring corporation), the portion of any Option that is unvested shall fully vest and become immediately exercisable in the event of a Change in Control Termination (as defined below). This right to accelerated vesting shall in no way (i) limit the Board's discretion to take the actions set forth in Section 10 of the Plan in the event of a Transaction, (ii) alter other terms of the Option Agreement(s), including extending the maximum term of the Award, or (iii) apply to any awards granted after the Effective Date, unless such future awards provide for such accelerated vesting.

As used herein, "Change in Control Termination" means termination of Optionee's service to the Company (or any surviving or acquiring corporation or entity) without Cause or Optionee's resignation for Good Reason (as defined below), in each case, only if such termination of service occurs during the period beginning on the date of the Change in Control and ending on the twelve-month anniversary of the Change in Control.

As used herein, "Good Reason" means any of the following actions taken by the Company (or any surviving or acquiring corporation or entity) without Optionee's consent: (i) any material diminution of Optionee's authority, duties or responsibilities; (ii) a material (greater than ten percent (10%)) reduction by the Company (or any surviving or acquiring corporation or entity) of Optionee's Base Salary except in the case of across-the-board salary reductions similarly affecting all or substantially all similarly-situated employees of the Company or any surviving or acquiring corporation or entity; (iii) a relocation of Optionee's place of employment to a location in excess of fifty (50) miles from the Company's last known principal place of employment; *provided, however,* with respect to each clause (i) through (iii), above, it will only be deemed Good Reason if (1) prior to Optionee's resignation, the Company (or any surviving or acquiring corporation or entity) has not previously notified the Optionee of its intention to terminate his/her employment; (2) the Company (or any surviving or acquiring corporation or

entity) is given written notice from Optionee within ninety (90) days following the first occurrence of a condition that Optionee considers to constitute Good Reason (with such notice including a description of the condition); (3) the Company (or any surviving or acquiring corporation or entity) fails to remedy such condition within thirty (30) days following such written notice, and (4) Optionee resigns from employment effective not later than fourteen (14) days after the end of the cure period. Notwithstanding the foregoing, any actions taken to accommodate a disability of Optionee or pursuant to the Family and Medical Leave Act or an applicable state leave law will not be a Good Reason for purposes of this Agreement.

This Amendment shall be deemed part of the Option Agreement(s) as of the Effective Date.

Amendment to Nonqualified Stock Option Agreement (Employees)
Issued under Amended and Restated Stock Incentive Plan

This Amendment to Nonqualified Stock Option Agreement (Employees) ("Amendment") issued under the Amended and Restated Stock Incentive Plan (the "Plan") of Entasis Therapeutics Holdings Inc. (the "Company") is made effective as of November 10, 2021 ("Effective Date") and modifies the outstanding Incentive Stock Options Agreement(s) (Senior Management) ("Option Agreements") existing as of the Effective Date between the Company and Optionee. Capitalized terms not explicitly defined in this Amendment or the Option Agreement(s), shall have the meanings set forth in the Plan.

Except as expressly modified by this Amendment, all of the terms of the Option Agreement(s) and the Plan shall remain in full force and effect.

The following provision is added as paragraph 14 to the Option Agreement(s):

14. Acceleration upon a Change in Control Termination. If after a Change in Control, some or all of Optionee's Options remain outstanding (for example, because they were substituted or assumed by the surviving or acquiring corporation), the portion of any Option that is unvested shall fully vest and become immediately exercisable in the event of a Change in Control Termination (as defined below). This right to accelerated vesting shall in no way (i) limit the Board's discretion to take the actions set forth in Section 10 of the Plan in the event of a Transaction, (ii) alter other terms of the Option Agreement(s), including extending the maximum term of the Award, or (iii) apply to any awards granted after the Effective Date, unless such future awards provide for such accelerated vesting.

As used herein, "Change in Control Termination" means termination of Optionee's service to the Company (or any surviving or acquiring corporation or entity) without Cause or Optionee's resignation for Good Reason (as defined below), in each case, only if such termination of service occurs during the period beginning on the date of the Change in Control and ending on the twelve-month anniversary of the Change in Control.

As used herein, "Good Reason" means any of the following actions taken by the Company (or any surviving or acquiring corporation or entity) without Optionee's consent: (i) any material diminution of Optionee's authority, duties or responsibilities; (ii) a material (greater than ten percent (10%)) reduction by the Company (or any surviving or acquiring corporation or entity) of Optionee's Base Salary except in the case of across-the-board salary reductions similarly affecting all or substantially all similarly-situated employees of the Company or any surviving or acquiring corporation or entity; (iii) a relocation of Optionee's place of employment to a location in excess of fifty (50) miles from the Company's last known principal place of employment; *provided*, *however,* with respect to each clause (i) through (iii), above, it will only be deemed Good Reason if (1) prior to Optionee's resignation, the Company (or any surviving or acquiring corporation or entity) has not previously notified the Optionee of its intention to terminate his/her employment; (2) the Company (or any surviving or acquiring corporation or

entity) is given written notice from Optionee within ninety (90) days following the first occurrence of a condition that Optionee considers to constitute Good Reason (with such notice including a description of the condition); (3) the Company (or any surviving or acquiring corporation or entity) fails to remedy such condition within thirty (30) days following such written notice, and (4) Optionee resigns from employment effective not later than fourteen (14) days after the end of the cure period. Notwithstanding the foregoing, any actions taken to accommodate a disability of Optionee or pursuant to the Family and Medical Leave Act or an applicable state leave law will not be a Good Reason for purposes of this Agreement.

This Amendment shall be deemed part of the Option Agreement(s) as of the Effective Date.

Amendment to Nonqualified Stock Option Agreement (Senior Management)
Issued under Amended and Restated Stock Incentive Plan

This Amendment to Nonqualified Stock Option Agreement (Senior Management) ("Amendment") issued under the Amended and Restated Stock Incentive Plan (the "Plan") of Entasis Therapeutics Holdings Inc. (the "Company") is made effective as of November 10, 2021 ("Effective Date") and modifies the outstanding Non-Qualified Stock Options Agreement(s) (Senior Management) ("Option Agreements") existing as of the Effective Date between the Company and Optionee. Capitalized terms not explicitly defined in this Amendment or the Option Agreement(s), shall have the meanings set forth in the Plan.

Except as expressly modified by this Amendment, all of the terms of the Option Agreement(s) and the Plan shall remain in full force and effect.

The following provision is added as paragraph 14 to the Option Agreement(s):

14. Acceleration upon a Change in Control Termination. If after a Change in Control, some or all of Optionee's Options remain outstanding (for example, because they were substituted or assumed by the surviving or acquiring corporation), the portion of any Option that is unvested shall fully vest and become immediately exercisable in the event of a Change in Control Termination (as defined below). This right to accelerated vesting shall in no way (i) limit the Board's discretion to take the actions set forth in Section 10 of the Plan in the event of a Transaction, (ii) alter other terms of the Option Agreement(s), including extending the maximum term of the Award, or (iii) apply to any awards granted after the Effective Date, unless such future awards provide for such accelerated vesting.

As used herein, "Change in Control Termination" means termination of Optionee's service to the Company (or any surviving or acquiring corporation or entity) without Cause or Optionee's resignation for Good Reason (as defined below), in each case, only if such termination of service occurs during the period beginning on the date of the Change in Control and ending on the twelve-month anniversary of the Change in Control.

As used herein, "Good Reason" means any of the following actions taken by the Company (or any surviving or acquiring corporation or entity) without Optionee's consent: (i) any material diminution of Optionee's authority, duties or responsibilities; (ii) a material (greater than ten percent (10%)) reduction by the Company (or any surviving or acquiring corporation or entity) of Optionee's Base Salary except in the case of across-the-board salary reductions similarly affecting all or substantially all similarly-situated employees of the Company or any surviving or acquiring corporation or entity; (iii) a relocation of Optionee's place of employment to a location in excess of fifty (50) miles from the Company's last known principal place of employment; *provided*, *however*, with respect to each clause (i) through (iii), above, it will only be deemed Good Reason if (1) prior to Optionee's resignation, the Company (or any surviving or acquiring corporation or entity) has not previously notified the Optionee of its intention to terminate his/her employment; (2) the Company (or any surviving or acquiring corporation or

entity) is given written notice from Optionee within ninety (90) days following the first occurrence of a condition that Optionee considers to constitute Good Reason (with such notice including a description of the condition); (3) the Company (or any surviving or acquiring corporation or entity) fails to remedy such condition within thirty (30) days following such written notice, and (4) Optionee resigns from employment effective not later than fourteen (14) days after the end of the cure period. Notwithstanding the foregoing, any actions taken to accommodate a disability of Optionee or pursuant to the Family and Medical Leave Act or an applicable state leave law will not be a Good Reason for purposes of this Agreement.

This Amendment shall be deemed part of the Option Agreement(s) as of the Effective Date.

Amendment to Option Agreement
Issued under 2018 Equity Incentive Plan

This Amendment to Option Agreement ("Amendment") issued under the 2018 Equity Incentive Plan (the "Plan") of Entasis Therapeutics Holdings Inc.'s (the "Company") is made effective as of November 10, 2021 ("Effective Date") and modifies the Option Agreement(s) existing as of the Effective Date between the Company and Optionholder. Capitalized terms not explicitly defined in this Amendment or the Option Agreement, shall the meaning set forth in the Plan.

Except as modified by this Amendment, all of the terms of the Option Agreement(s), Grant Notice(s) and the Plan shall remain in full force and effect.

The following provision is added as paragraph 20 to the Option Agreement(s):

20. Acceleration upon Change in Control. Effective as of the later of Optionholder's Change in Control Termination (as defined below) date or the effective date of the Change in Control, all outstanding stock options covering the Company's Common Stock that are held by Optionholder as of immediately prior to the Change in Control Termination date, to the extent such awards are subject to time-based vesting requirements, will be accelerated in full and will become immediately fully vested and exercisable. Optionholder's stock options will remain outstanding following Optionholder's Change in Control Termination date if and to the extent necessary to give effect to this Section 20 subject to earlier termination under the terms of the Plan and Option Agreement, including but not limited to the original maximum term of the Award (without regard to Optionholder's termination). This right to accelerated vesting shall in no way (i) limit the Board's discretion to take the actions set forth in Section 9(c) of the Plan (Transaction) in the event of a Transaction, (ii) alter other terms of the Option Agreement, including the maximum term of the Award, or (iii) apply to any awards granted after the Effective Date, unless such future awards provide for such accelerated vesting.

As used herein, "Change in Control Termination" means termination of Optionholder's employment by the Company (or any surviving or acquiring corporation or entity) within twelve months of a Change in Control where such termination is without Cause or results from Optionholder's resignation for Good Reason.

As used herein, "Good Reason" means any of the following actions taken by the Company (or any surviving or acquiring corporation or entity) without Optionholder's consent: (i) any material diminution of Optionholder's authority, duties or responsibilities; (ii) a material (greater than ten percent (10%)) reduction by the Company (or any surviving or acquiring corporation or entity) of Optionholder's Base Salary except in the case of across-the-board salary reductions similarly affecting all or substantially all similarly-situated employees of the Company or any surviving or acquiring corporation or entity); (iii) a relocation of Optionholder's place of employment to a location in excess of fifty (50) miles from the Company's last known principal place of employment; *provided*, *however*, that it will only be deemed Good Reason if (1) prior to Optionholder's resignation, the Company (or any surviving or acquiring corporation

or entity) has not previously notified the Optionholder of its intention to terminate his/her employment; (2) the Company (or any surviving or acquiring corporation or entity) is given written notice from Optionholder within ninety (90) days following the first occurrence of a condition that Optionholder considers to constitute Good Reason (with such notice including a description of the condition); (3) the Company (or any surviving or acquiring corporation or entity) fails to remedy such condition within thirty (30) days following such written notice, and (4) Optionholder resigns from employment effective not later than fourteen (14) days after the end of the cure period. Notwithstanding the foregoing, any actions taken to accommodate a disability of Optionholder or pursuant to the Family and Medical Leave Act or an applicable state leave law will not be a Good Reason for purposes of this Agreement.

This Amendment shall be deemed part of the Option Agreement as of the Effective Date.

Amendment to Restricted Stock Unit Grant Agreement
Issued under 2018 Equity Incentive Plan

This Amendment to Restricted Stock Unit Grant Agreement ("Amendment") issued under the 2018 Equity Incentive Plan (the "Plan") of Entasis Therapeutics Holdings Inc. (the "Company") is made effective as of November 10, 2021 ("Effective Date") and modifies the outstanding Restricted Stock Unit Agreement(s) ("RSU Agreements") existing as of the Effective Date between the Company and Participant. Capitalized terms not explicitly defined in this Amendment or the Option Agreement, shall have the meanings set forth in the Plan.

Except as expressly modified by this Amendment, all of the terms of the RSU Agreement(s), Grant Notice(s) and the Plan shall remain in full force and effect.

The following provision is added as paragraph 24 to the RSU Agreement(s):

24. Acceleration upon a Change in Control Termination. If after a Change in Control, some or all of Participants restricted stock units ("RSUs") remain outstanding (for example, because they were substituted or assumed by the surviving or acquiring corporation), the portion of any RSU that is unvested shall fully vest and become immediately exercisable in the event of a Change in Control Termination (as defined below). This right to accelerated vesting shall in no way (i) limit the Board's discretion to take the actions set forth in Section 9(c) of the Plan in the event of a Transaction, (ii) alter other terms of the RSU Agreement(s), or (iii) apply to any awards granted after the Effective Date, unless such future awards provide for such accelerated vesting.

As used herein, "Change in Control Termination" means termination of Participant's service to the Company (or any surviving or acquiring corporation or entity) without Cause or Participant's resignation for Good Reason (as defined below), in each case, only if such termination of service occurs during the period beginning on the date of the Change in Control and ending on the twelve-month anniversary of the Change in Control.

As used herein, "Good Reason" means any of the following actions taken by the Company (or any surviving or acquiring corporation or entity) without Participant's consent: (i) any material diminution of Participant's authority, duties or responsibilities; (ii) a material (greater than ten percent (10%)) reduction by the Company (or any surviving or acquiring corporation or entity) of Participant's Base Salary except in the case of across-the-board salary reductions similarly affecting all or substantially all similarly-situated employees of the Company or any surviving or acquiring corporation or entity; (iii) a relocation of Participant's place of employment to a location in excess of fifty (50) miles from the Company's last known principal place of employment; *provided*, *however*, with respect to each clause (i) through (iii), above, it will only be deemed Good Reason if (1) prior to Participant's resignation, the Company (or any surviving or acquiring corporation or entity) has not previously notified the Participant of its intention to terminate his/her employment; (2) the Company (or any surviving or acquiring corporation or entity) is given written notice from Participant within ninety (90) days following

the first occurrence of a condition that Participant considers to constitute Good Reason (with such notice including a description of the condition); (3) the Company (or any surviving or acquiring corporation or entity) fails to remedy such condition within thirty (30) days following such written notice, and (4) Participant resigns from employment effective not later than fourteen (14) days after the end of the cure period. Notwithstanding the foregoing, any actions taken to accommodate a disability of Participant or pursuant to the Family and Medical Leave Act or an applicable state leave law will not be a Good Reason for purposes of this Agreement.

This Amendment shall be deemed part of the RSU Agreement(s) as of the Effective Date.

OPTION AGREEMENT (AMENDED) (EMPLOYEES/D & Os)
(2018 EQUITY INCENTIVE PLAN)
(INCENTIVE STOCK OPTION OR NONSTATUTORY STOCK OPTION)

Pursuant to your Stock Option Grant Notice ("***Grant Notice***") and this Option Agreement (Amended), Entasis Therapeutics Holdings Inc. (the "***Company***") has granted you an option under its 2018 Equity Incentive Plan (the "***Plan***") to purchase the number of shares of the Company's Common Stock indicated in your Grant Notice at the exercise price indicated in your Grant Notice. The option is granted to you effective as of the date of grant set forth in the Grant Notice (the "***Date of Grant***"). If there is any conflict between the terms in this Option Agreement and the Plan, the terms of the Plan will control. Capitalized terms not explicitly defined in this Option Agreement or in the Grant Notice but defined in the Plan will have the same definitions as in the Plan.

The details of your option, in addition to those set forth in the Grant Notice and the Plan, are as follows:

1. VESTING. Subject to the provisions contained herein, your option will vest as provided in your Grant Notice. Vesting will cease upon the termination of your Continuous Service.

2. NUMBER OF SHARES AND EXERCISE PRICE. The number of shares of Common Stock subject to your option and your exercise price per share in your Grant Notice will be adjusted for Capitalization Adjustments.

3. EXERCISE RESTRICTION FOR NON-EXEMPT EMPLOYEES. If you are an Employee eligible for overtime compensation under the Fair Labor Standards Act of 1938, as amended (that is, a "***Non-Exempt Employee***"), and except as otherwise provided in the Plan, you may not exercise your option until you have completed at least six (6) months of Continuous Service measured from the Date of Grant, even if you have already been an employee for more than six (6) months. Consistent with the provisions of the Worker Economic Opportunity Act, you may exercise your option as to any vested portion prior to such six (6) month anniversary in the case of (i) your death or disability, (ii) a Corporate Transaction in which your option is not assumed, continued or substituted, (iii) a Change in Control or (iv) your termination of Continuous Service on your "retirement" (as defined in the Company's benefit plans).

4. METHOD OF PAYMENT. You must pay the full amount of the exercise price for the shares you wish to exercise. You may pay the exercise price in cash or by check, bank draft or money order payable to the Company or in any other manner ***permitted by your Grant Notice,*** which may include one or more of the following:

(a) Provided that at the time of exercise the Common Stock is publicly traded, pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board that, prior to the issuance of Common Stock, results in either the receipt of cash (or check) by the Company or the receipt of irrevocable instructions to pay the aggregate exercise price to

the Company from the sales proceeds. This manner of payment is also known as a “broker-assisted exercise”, “same day sale”, or “sell to cover”.

(b) Provided that at the time of exercise the Common Stock is publicly traded, by delivery to the Company (either by actual delivery or attestation) of already-owned shares of Common Stock that are owned free and clear of any liens, claims, encumbrances or security interests, and that are valued at Fair Market Value on the date of exercise. “Delivery” for these purposes, in the sole discretion of the Company at the time you exercise your option, will include delivery to the Company of your attestation of ownership of such shares of Common Stock in a form approved by the Company. You may not exercise your option by delivery to the Company of Common Stock if doing so would violate the provisions of any law, regulation or agreement restricting the redemption of the Company’s stock.

(c) If this option is a Nonstatutory Stock Option, subject to the consent of the Company at the time of exercise, by a “net exercise” arrangement pursuant to which the Company will reduce the number of shares of Common Stock issued upon exercise of your option by the largest whole number of shares with a Fair Market Value that does not exceed the aggregate exercise price. You must pay any remaining balance of the aggregate exercise price not satisfied by the “net exercise” in cash or other permitted form of payment. Shares of Common Stock will no longer be outstanding under your option and will not be exercisable thereafter if those shares (i) are used to pay the exercise price pursuant to the “net exercise,” (ii) are delivered to you as a result of such exercise, and (iii) are withheld to satisfy your tax withholding obligations.

5. WHOLE SHARES. You may exercise your option only for whole shares of Common Stock.

6. SECURITIES LAW COMPLIANCE. In no event may you exercise your option unless the shares of Common Stock issuable upon exercise are then registered under the Securities Act or, if not registered, the Company has determined that your exercise and the issuance of the shares would be exempt from the registration requirements of the Securities Act. The exercise of your option also must comply with all other applicable laws and regulations governing your option, and you may not exercise your option if the Company determines that such exercise would not be in material compliance with such laws and regulations (including any restrictions on exercise required for compliance with Treas. Reg. 1.401(k)-1(d)(3), if applicable).

7. TERM. You may not exercise your option before the Date of Grant or after the expiration of the option’s term. The term of your option expires, subject to the provisions of Section 5(h) of the Plan, upon the earliest of the following:

(a) immediately upon the termination of your Continuous Service for Cause;

(b) three (3) months after the termination of your Continuous Service for any reason other than Cause, your Disability or your death (except as otherwise provided in Section 7(d) below); *provided, however,* that if during any part of such three (3) month period your option is not exercisable solely because of the condition set forth in the section above

regarding “Securities Law Compliance,” your option will not expire until the earlier of the Expiration Date or until it has been exercisable for an aggregate period of three (3) months after the termination of your Continuous Service; *provided further,* if during any part of such three (3) month period, the sale of any Common Stock received upon exercise of your option would violate the Company’s insider trading policy, then your option will not expire until the earlier of the Expiration Date or until it has been exercisable for an aggregate period of three (3) months after the termination of your Continuous Service during which the sale of the Common Stock received upon exercise of your option would not be in violation of the Company’s insider trading policy. Notwithstanding the foregoing, if (i) you are a Non-Exempt Employee, (ii) your Continuous Service terminates within six (6) months after the Date of Grant, and (iii) you have vested in a portion of your option at the time of your termination of Continuous Service, your option will not expire until the earlier of (x) the later of (A) the date that is seven (7) months after the Date of Grant, and (B) the date that is three (3) months after the termination of your Continuous Service, and (y) the Expiration Date;

(c) twelve (12) months after the termination of your Continuous Service due to your Disability (except as otherwise provided in Section 7(d) below);

(d) eighteen (18) months after your death if you die either during your Continuous Service or within three (3) months after your Continuous Service terminates for any reason other than Cause;

(e) the Expiration Date indicated in your Grant Notice; or

(f) the day before the tenth (10th) anniversary of the Date of Grant.

If your option is an Incentive Stock Option, note that to obtain the federal income tax advantages associated with an Incentive Stock Option, the Code requires that at all times beginning on the Date of Grant and ending on the day three (3) months before the date of your option’s exercise, you must be an employee of the Company or an Affiliate, except in the event of your death or Disability. The Company has provided for extended exercisability of your option under certain circumstances for your benefit but cannot guarantee that your option will necessarily be treated as an Incentive Stock Option if you continue to provide services to the Company or an Affiliate as a Consultant or Director after your employment terminates or if you otherwise exercise your option more than three (3) months after the date your employment with the Company or an Affiliate terminates.

8. EXERCISE.

(a) You may exercise the vested portion of your option (and the unvested portion of your option if your Grant Notice so permits) during its term by (i) delivering a Notice of Exercise (in a form designated by the Company) or completing such other documents and/or procedures designated by the Company for exercise and (ii) paying the exercise price and any applicable withholding taxes to the Company’s Secretary, stock plan administrator, or such other person as the Company may designate, together with such additional documents as the Company may then require.

(b) By exercising your option you agree that, as a condition to any exercise of your option, the Company may require you to enter into an arrangement providing for the payment by you to the Company of any tax withholding obligation of the Company arising by reason of (i) the exercise of your option, (ii) the lapse of any substantial risk of forfeiture to which the shares of Common Stock are subject at the time of exercise, or (iii) the disposition of shares of Common Stock acquired upon such exercise.

(c) If your option is an Incentive Stock Option, by exercising your option you agree that you will notify the Company in writing within fifteen (15) days after the date of any disposition of any of the shares of the Common Stock issued upon exercise of your option that occurs within two (2) years after the Date of Grant or within one (1) year after such shares of Common Stock are transferred upon exercise of your option.

9. TRANSFERABILITY. Except as otherwise provided in this Section 9, your option is not transferable, except by will or by the laws of descent and distribution, and is exercisable during your life only by you.

(a) Certain Trusts. Upon receiving written permission from the Board or its duly authorized designee, you may transfer your option to a trust if you are considered to be the sole beneficial owner (determined under Section 671 of the Code and applicable state law) while the option is held in the trust. You and the trustee must enter into transfer and other agreements required by the Company.

(b) Domestic Relations Orders. Upon receiving written permission from the Board or its duly authorized designee, and provided that you and the designated transferee enter into transfer and other agreements required by the Company, you may transfer your option pursuant to the terms of a domestic relations order, official marital settlement agreement or other divorce or separation instrument as permitted by Treasury Regulation 1.421-1(b)(2) that contains the information required by the Company to effectuate the transfer. You are encouraged to discuss the proposed terms of any division of this option with the Company prior to finalizing the domestic relations order or marital settlement agreement to help ensure the required information is contained within the domestic relations order or marital settlement agreement. If this option is an Incentive Stock Option, this option may be deemed to be a Nonstatutory Stock Option as a result of such transfer.

(c) Beneficiary Designation. Upon receiving written permission from the Board or its duly authorized designee, you may, by delivering written notice to the Company, in a form approved by the Company and any broker designated by the Company to handle option exercises, designate a third party who, on your death, will thereafter be entitled to exercise this option and receive the Common Stock or other consideration resulting from such exercise. In the absence of such a designation, your executor or administrator of your estate will be entitled to exercise this option and receive, on behalf of your estate, the Common Stock or other consideration resulting from such exercise.

10. OPTION NOT A SERVICE CONTRACT. Your option is not an employment or service contract, and nothing in your option will be deemed to create in any way whatsoever any obligation on your part to continue in the employ of the Company or an Affiliate, or of the Company or an Affiliate to continue your employment. In addition, nothing in your option will obligate the Company or an Affiliate, their respective stockholders, boards of directors, officers or employees to continue any relationship that you might have as a Director or Consultant for the Company or an Affiliate.

11. WITHHOLDING OBLIGATIONS.

(a) At the time you exercise your option, in whole or in part, and at any time thereafter as requested by the Company, you hereby authorize withholding from payroll and any other amounts payable to you, and otherwise agree to make adequate provision for (including by means of a "same day sale" pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board to the extent permitted by the Company), any sums required to satisfy the federal, state, local and foreign tax withholding obligations of the Company or an Affiliate, if any, which arise in connection with the exercise of your option.

(b) If this option is a Nonstatutory Stock Option, then upon your request and subject to approval by the Company, and compliance with any applicable legal conditions or restrictions, the Company may withhold from fully vested shares of Common Stock otherwise issuable to you upon the exercise of your option a number of whole shares of Common Stock having a Fair Market Value, determined by the Company as of the date of exercise, not in excess of the minimum amount of tax required to be withheld by law (or such lower amount as may be necessary to avoid classification of your option as a liability for financial accounting purposes). Notwithstanding the filing of such election, shares of Common Stock shall be withheld solely from fully vested shares of Common Stock determined as of the date of exercise of your option that are otherwise issuable to you upon such exercise. Any adverse consequences to you arising in connection with such share withholding procedure shall be your sole responsibility.

(c) You may not exercise your option unless the tax withholding obligations of the Company and/or any Affiliate are satisfied. Accordingly, you may not be able to exercise your option when desired even though your option is vested, and the Company will have no obligation to issue a certificate for such shares of Common Stock or release such shares of Common Stock from any escrow provided for herein, if applicable, unless such obligations are satisfied.

12. TAX CONSEQUENCES. You hereby agree that the Company does not have a duty to design or administer the Plan or its other compensation programs in a manner that minimizes your tax liabilities. You will not make any claim against the Company, or any of its Officers, Directors, Employees or Affiliates related to tax liabilities arising from your option or your other compensation. In particular, you acknowledge that this option is exempt from Section 409A of the Code only if the exercise price per share specified in the Grant Notice is at least equal to the "fair market value" per share of the Common Stock on the Date of Grant and there is no other impermissible deferral of compensation associated with the option.

13. NOTICES. Any notices provided for in your option or the Plan will be given in writing (including electronically) and will be deemed effectively given upon receipt or, in the case of notices delivered by mail by the Company to you, five (5) days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. The Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this option by electronic means or to request your consent to participate in the Plan by electronic means. By accepting this option, you consent to receive such documents by electronic delivery and to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

14. GOVERNING PLAN DOCUMENT. Your option is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your option, and is further subject to all interpretations, amendments, rules and regulations, which may from time to time be promulgated and adopted pursuant to the Plan. If there is any conflict between the provisions of your option and those of the Plan, the provisions of the Plan will control. In addition, your option (and any compensation paid or shares issued under your option) is subject to recoupment in accordance with The Dodd—Frank Wall Street Reform and Consumer Protection Act and any implementing regulations thereunder, any clawback policy adopted by the Company and any compensation recovery policy otherwise required by applicable law.

15. OTHER DOCUMENTS. You hereby acknowledge receipt of and the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's policy permitting certain individuals to sell shares only during certain "window" periods and the Company's insider trading policy, in effect from time to time.

16. EFFECT ON OTHER EMPLOYEE BENEFIT PLANS. The value of this option will not be included as compensation, earnings, salaries, or other similar terms used when calculating your benefits under any employee benefit plan sponsored by the Company or any Affiliate, except as such plan otherwise expressly provides. The Company expressly reserves its rights to amend, modify, or terminate any of the Company's or any Affiliate's employee benefit plans.

17. VOTING RIGHTS. You will not have voting or any other rights as a stockholder of the Company with respect to the shares to be issued pursuant to this option until such shares are issued to you. Upon such issuance, you will obtain full voting and other rights as a stockholder of the Company. Nothing contained in this option, and no action taken pursuant to its provisions, will create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

18. SEVERABILITY. If all or any part of this Option Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity will not invalidate any portion of this Option Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Option Agreement (or part of such a Section) so declared to be unlawful or invalid shall, if possible, be construed in a manner which will give effect to the terms

of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

19. ACCELERATION UPON CHANGE IN CONTROL. Effective as of the later of your Change in Control Termination (as defined below) date or the effective date of the Change in Control, the stock options covering the Company's Common Stock that are held by you as of immediately prior to the Change in Control Termination date, to the extent such awards are subject to time-based vesting requirements, will be accelerated in full and will become immediately fully vested and exercisable. Your stock options will remain outstanding following your Change in Control Termination date if and to the extent necessary to give effect to this Section 20 subject to earlier termination under the terms of the Plan and this Option Agreement (Amended), including but not limited to the original maximum term of the Award (without regard to your termination). This right to accelerated vesting shall in no way (i) limit the Board's discretion to take the actions set forth in Section 9(c) of the Plan (Transaction) in the event of a Transaction, (ii) alter other terms of the Option Agreement, including the maximum term of the Award, or (iii) apply to any awards granted after the Effective Date, unless such future awards provide for such accelerated vesting.

As used herein: "Change in Control Termination" means termination of your employment by the Company (or any surviving or acquiring corporation or entity) within twelve months of a Change in Control where such termination is without Cause or results from your resignation for Good Reason; and "Good Reason" means any of the following actions taken by the Company (or any surviving or acquiring corporation or entity) without your consent: (i) any material diminution of your authority, duties or responsibilities; (ii) a material (greater than ten percent (10%)) reduction by the Company (or any surviving or acquiring corporation or entity) of your Base Salary except in the case of across-the-board salary reductions similarly affecting all or substantially all similarly-situated employees of the Company or any surviving or acquiring corporation or entity); (iii) a relocation of your place of employment to a location in excess of fifty (50) miles from the Company's last known principal place of employment; *provided*, *however*, that it will only be deemed Good Reason if (1) prior to your resignation, the Company (or any surviving or acquiring corporation or entity) has not previously notified you of its intention to terminate your employment; (2) the Company (or any surviving or acquiring corporation or entity) is given written notice from you within ninety (90) days following the first occurrence of a condition that you consider to constitute Good Reason (with such notice including a description of the condition); (3) the Company (or any surviving or acquiring corporation or entity) fails to remedy such condition within thirty (30) days following such written notice, and (4) you resign from employment effective not later than fourteen (14) days after the end of the cure period. Notwithstanding the foregoing, any actions taken to accommodate a disability of you or pursuant to the Family and Medical Leave Act or an applicable state leave law will not be a Good Reason for purposes of this Agreement.

20. MISCELLANEOUS.

(a) The rights and obligations of the Company under your option will be transferable to any one or more persons or entities, and all covenants and agreements hereunder will inure to the benefit of, and be enforceable by the Company's successors and assigns.

(b) You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your option.

(c) You acknowledge and agree that you have reviewed your option in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your option, and fully understand all provisions of your option.

(d) This Option Agreement will be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

(e) All obligations of the Company under the Plan and this Option Agreement will be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

This Option Agreement will be deemed to be signed by you upon the signing by you of the Stock Option Grant Notice to which it is attached.

ENTASIS THERAPEUTICS HOLDINGS INC.

2018 EQUITY INCENTIVE PLAN
RESTRICTED STOCK UNIT GRANT AGREEMENT (EMPLOYEE/D & O)

Pursuant to the Restricted Stock Unit Grant notice (the "**Grant Notice**") and this Restricted Stock Unit Award Agreement (the "**Agreement**"), Entasis Therapeutics Holdings Inc. (the "**Company**") has awarded you ("**Participant**") a Restricted Stock Unit Award (the "**Award**") pursuant to the Company's 2018 Equity Incentive Plan (the "**Plan**") to be issued the number of Restricted Stock Units/shares indicated in the Grant Notice. Capitalized terms not explicitly defined in this Agreement or the Grant Notice shall have the same meanings given to them in the Plan. The terms of your Award, in addition to those set forth in the Grant Notice and the Plan, are as follows:

1. **GRANT OF THE AWARD.** This Award represents the right to be issued on a future date one (1) share of Common Stock for each Restricted Stock Unit that vests on the applicable vesting date(s) (subject to any adjustment under Section 3 below) as indicated in the Grant Notice. As of the Date of Grant, the Company will credit to a bookkeeping account maintained by the Company for your benefit (the "**Account**") the number of Restricted Stock Units/shares of Common Stock subject to the Award. Notwithstanding the foregoing, the Company reserves the right to issue you the cash equivalent of Common Stock, in part or in full satisfaction of the delivery of Common Stock in connection with the vesting of the Restricted Stock Units, and, to the extent applicable, references in this Agreement and the Grant Notice to Common Stock issuable in connection with your Restricted Stock Units will include the potential issuance of its cash equivalent pursuant to such right. This Award was granted in consideration of your services to the Company.

2. **VESTING.** Subject to the limitations contained herein and in the Plan, your Award will vest, if at all, in accordance with the vesting schedule provided in the Grant Notice, provided that vesting will cease upon the termination of your Continuous Service. Upon such termination of your continuous Service, the Restricted Stock Units/shares of Common Stock credited to the Account that were not vested on the date of such termination will be forfeited at no cost to the Company and you will have no further right, title or interest in or to such underlying shares of Common Stock.

3. **NUMBER OF SHARES.** The number of Restricted Stock Units/shares subject to your Award may be adjusted from time to time for Capitalization Adjustments as provided in the Plan. Any additional Restricted Stock Units, shares, cash or other property that becomes subject to the Award pursuant to this Section 3, if any, shall be subject, in a manner determined by the Board, to the same forfeiture restrictions, restrictions on transferability, and time and manner of delivery as applicable to the other Restricted Stock Units and shares covered by your Award. Notwithstanding the provisions of this Section 3, no fractional shares or right for fractional shares of Common Stock shall be created pursuant to this Section 3. The Company will, in its discretion, determine an equivalent benefit for any fractional shares or fractional shares that might be created by the adjustments referred to in this Section 3.

4. **SECURITIES LAW COMPLIANCE.** You may not be issued any Common Stock under your Award unless the shares of Common Stock underlying the Restricted Stock Units are either (i) then registered under the Securities Act or (ii) the Company has determined that such issuance would be exempt from the registration requirements of the Securities Act. Your Award must also comply with other applicable laws and regulations governing the Award, and you shall not receive such Common Stock if the Company determines that such receipt would not be in material compliance with such laws and regulations.

5. **TRANSFER RESTRICTIONS.** Prior to the time that shares of Common Stock have been delivered to you, you may not transfer, pledge, sell or otherwise dispose of this Award or the shares issuable in respect of your Award, except as expressly provided in this Section 5. For example, you may not use shares that may be issued in respect of your Restricted Stock Units as security for a loan. The restrictions on transfer set forth herein will lapse upon delivery to you of shares in respect of your vested Restricted Stock Units.

(a) **DEATH.** Your Award is transferable by will and by the laws of descent and distribution. At your death, vesting of your Award will cease and your executor or administrator of your estate shall be entitled to receive, on behalf of your estate, any Common Stock or other consideration that was vested but was not issued before your death.

(b) **DOMESTIC RELATIONS ORDERS.** Upon receiving written permission from the Board or its duly authorized designed, and provided that you and the designated transferee enter into transfer and other agreements required by the Company, you may transfer your right to receive the distribution of Common Sock or other consideration hereunder, pursuant to a domestic relations order, marital settlement agreement or other divorce or separation instrument as permitted by applicable law that contains the information required by the Company to effectuate the transfer. You are encouraged to discuss the proposed terms of any division of this Award with the Company General Counsel prior to finalizing the domestic relations order or marital settlement agreement to verify that you may make such transfer, and if so, to help ensure the required information is contained within the domestic relations order or marital settlement agreement.

6. **DATE OF ISSUANCE.**

(a) The issuance of shares in respect of the Restricted Stock Units is intended to comply with the Treasury Regulations Section 1.409A-1(b)(4) and will be construed and administered in such a manner.

Subject to the satisfaction of the Withholding Taxes set forth in Section 11 of this Agreement, in the event one or more Restricted Stock Units vests, the Company shall issue to you one (1) share of Common Stock for each Restricted Stock Unit that vests on the applicable vesting date(s) (subject to any adjustment under Section 3 above). Each issuance date determined by this paragraph is referred to as an “Original Issuance Date”.

(b) If the Original Issuance Date falls on a date that is not a business day, delivery shall instead occur on the next following business day. In addition, if

(i) the Original Issuance Date does not occur (1) during an "open window period" applicable to you, as determined by the Company in accordance with the Company's then-effective policy on trading in the Company securities, or (2) on a date when you are otherwise permitted to sell shares of Common Stock on an established stock exchange or stock market (including but not limited to under a previously established written trading plan that meets the requirements of Rule 10b5-1 under the Exchange Act and was entered into in compliance with the Company's policies (a "**10b5-1 Plan**")), *and*

(ii) either (1) Withholding Taxes do not apply, or (2) Withholding Taxes apply and the Company decides, prior to the Original Issuance Date, (A) not to satisfy the Withholding Taxes by withholding shares of Common Stock from the shares otherwise due, on the Original Issuance Date, to you under this Award, and (B) not to permit you to then effect a sale on the market under a 10b5-1 Plan and (C) not to permit you to pay your Withholding Taxes in cash, then the shares that would otherwise be issued to you on the Original Issuance Date will not be delivered on such Original Issuance Date and will instead be delivered on the first business day when you are not prohibited from selling shares of the Company's Common Stock in the open public market, but in no event later than (a) December 31 of the calendar year in which the Original Issuance Date occurs (that is, the last day of your taxable year in which the Original Issuance Date occurs), or (b) if and only if permitted in a manner that complies with Treasury Regulations Section 1.409A-1(b)(4), no later than the date that is the 15th day of the third calendar month of the applicable year following the year in which the shares of Common Stock under this Award are no longer subject to a "substantial risk of forfeiture" within the meaning of Treasury Regulations Section 1.409A-1(d) (such applicable date under (a) or (b), the "**Issuance Deadline**").

(c) The form of delivery (e.g., a stock certificate or electronic entry evidencing such shares) shall be determined by the Company. If the Company elects to issue you cash in part or in full satisfaction of the shares of Common Stock issuable upon vesting of your Restricted Stock Units, then the foregoing provisions of this Section 6(b) will not apply and such cash will be paid to you in a lump sum at any time on or after the vesting date of your Restricted Stock Units, but in no event later than the Issuance Deadline.

7. **DIVIDENDS.** You shall receive no benefit or adjustment to your Award with respect to any cash dividend, stock dividend or other distribution except as provided in the Plan with respect to a Capitalization Adjustment.

8. **RESTRICTIVE LEGENDS.** The shares of Common Stock issued under your Award shall be endorsed with appropriate legends as determined by the Company.

9. **EXECUTION OF DOCUMENTS.** You hereby acknowledge and agree that the manner selected by the Company by which you indicate your consent to your Grant Notice is also deemed to be your execution of your Grant Notice and of this Agreement. You further agree that

such manner of indicating consent may be relied upon as your signature for establishing your execution of any documents to be executed in the future in connection with your Award.

10. **AWARD NOT A SERVICE CONTRACT.**

(a) Nothing in this Agreement (including, but not limited to, the vesting of your Award or the issuance of the shares in respect of your Award), the Plan or any covenant of good faith and fair dealing that may be found implicit in this Agreement or the Plan shall: (i) confer upon you any right to continue in the employ or service of, or affiliation with, the Company or an Affiliate; (ii) constitute any promise or commitment by the Company or any Affiliate regarding the fact or nature of future positions, future work assignments, future compensation or any other term or condition of employment or affiliation; (iii) confer any right or benefit under this Agreement or the Plan unless such right or benefit has specifically accrued under the terms of this Agreement or Plan; or (iv) deprive the Company or an Affiliate of the right to terminate you at will and without regard to any future vesting opportunity that you may have.

(b) By accepting this Award, you acknowledge and agree that the right to continue vesting in the Award pursuant to the vesting schedule provided in the Grant Notice may not be earned unless (in addition to any other conditions described in the Grant Notice and this Agreement) you continue as an employee, director or consultant at the will of the Company and Affiliate, as applicable (not through the act of being hired, being granted this Award or any other award or benefit) and that the Company has the right to reorganize, sell, spin-out or otherwise restructure one or more of its businesses or Affiliates at any time or from time to time, as it deems appropriate (a "**Reorganization**"). You acknowledge and agree that such a Reorganization could result in the termination of your Continuous Service, or the termination of Affiliate status of your employer and the loss of benefits available to you under this Agreement, including but not limited to, the termination of the right to continue vesting in the Award. You further acknowledge and agree that this Agreement, the Plan, the transactions contemplated hereunder and the vesting schedule or any covenant of good faith and fair dealing that may be found implicit in any of them do not constitute an express or implied promise of continued engagement as an employee, director or consultant of the Company or an Affiliate for the term of this Agreement, for any period, or at all, and shall not interfere in any way with your right or the right of the Company or an Affiliate to terminate your status as a service provider at any time, with or without cause or notice.

11. **WITHHOLDING TAXES.**

(a) On each vesting date, and on or before the time you receive a distribution of the shares of Common Stock in respect of your Restricted Stock Units, and at any other time as reasonably requested by the Company in accordance with applicable tax laws, you hereby authorize any required withholding from the Common Stock issuable to you and/or otherwise agree to make adequate provision, including in cash, for any sums required to satisfy the federal, state, local and foreign tax withholding obligations of the Company or any Affiliate that arise in connection with your Award (the "Withholding Taxes").

(b) By accepting this Award, you acknowledge and agree that the Company or any Affiliate may, in its sole discretion, satisfy all or any portion of the Withholding Taxes obligation relating to your Award by any of the following means or by a combination of such means: (i) withholding from any compensation otherwise payable to you by the Company or an Affiliate; (ii) causing you to tender a cash payment; (iii) permitting or requiring you to enter into a "same day sale" commitment, if applicable, with a broker-dealer that is a member of the Financial Industry Regulatory Authority (a "FINRA Dealer") whereby you irrevocably elect to sell a portion of the shares to be delivered in connection with your Restricted Stock Units to satisfy the Withholding Taxes and whereby the FINRA Dealer irrevocably commits to forward the proceeds necessary to satisfy the Withholding Taxes directly to the Company and/or its Affiliates; or (iv) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to you in connection with the Award with a Fair Market Value (measured as of the date shares of Common Stock are issued pursuant to Section 6) not in excess of the maximum amount of tax that may be required to be withheld by law (or such other amount as may be permitted while still avoiding classification of the Award as a liability for financing accounting purposes); and, provided, further that to the extent necessary to qualify for an exemption from application of Section 16(b) of the Exchange Act, if applicable, such share withholding procedure will be subject to the express prior approval of the Board or the Company's Compensation Committee.

(c) Unless the Withholding Taxes are satisfied, the Company shall have no obligation to deliver to you any Common Stock or any other consideration pursuant to this Award.

(d) In the event the Withholding Taxes arise prior to the delivery to you of Common Stock or it is determined after the delivery of Common Stock to you that the amount of the Withholding Taxes was greater than the amount withheld by the Company, you agree to indemnify and hold the Company harmless from any failure by the Company to withhold the proper amount.

12. **TAX CONSEQUENCES.** The Company has no duty or obligation to minimize the tax consequences to you of this Award and shall not be liable to you for any adverse tax consequences to you arising in connection with this Award. You acknowledge that the Company is not making representations or undertakings regarding the treatment of your Award in connection with any aspect of your Award, including, but not limited to, the grant, vesting or settlement of the Award, the subsequent sale of shares of Common Stock acquired pursuant to such settlement and the receipt of any dividends and/or any dividend equivalent payments. You are hereby advised to consult with your own personal tax, financial and/or legal advisors regarding the tax consequences of this Award and by signing the Grant Notice, you have agreed that you have done so or knowingly and voluntarily declined to do so. You understand that you (and not the Company) shall be responsible for your own tax liability that may arise as a result of this investment or the transactions contemplated by this Agreement.

13. **UNRESTRICTED OBLIGATION.** Your Award is unfunded, and as a holder of a vested Award, you shall be considered an unsecured creditor of the Company with respect to the Company's obligation, if any, to issue shares or other property pursuant to this Agreement. You shall not have voting or any other rights as a stockholder of the Company with respect to the

shares to be issued pursuant to this Agreement until such shares are issued to you pursuant to Section 6 of this Agreement. Upon such issuance, you will obtain full voting and other rights as a stockholder of the Company. Nothing contained in this Agreement, and no action taken pursuant to its provisions, shall create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

14. **NO ADVICE REGARDING GRANT.** The Company is not providing any tax, legal or financial advice, nor is the Company making any recommendations regarding your participation in the Plan, or your acquisition or sale of the underlying shares of Common Stock. You are hereby advised to consult with your own personal tax, financial and/or legal advisors regarding the taxes arising in connection with the Award and by accepting the Award, you have agreed that you have done so or knowingly and voluntarily declined to do so.

15. **NOTICES.** Any notice or request required or permitted hereunder shall be given in writing (including electronically) and will be deemed effectively given upon receipt or, in the case of notices delivered by mail by the Company to you, five (5) days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. The Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this Award by electronic means or to request your consent to participate in the Plan by electronic means. By accepting this Award, you consent to receive such documents by electronic delivery and to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

16. **HEADINGS.** The headings of the Sections in this Agreement are inserted for convenience only and shall not be deemed to constitute a part of this Agreement or to affect the meaning of this Agreement.

17. **ACCELERATION UPON CHANGE IN CONTROL.** If after a Change in Control, some or all of your restricted stock units ("RSUs") remain outstanding (for example, because they were substituted or assumed by the surviving or acquiring corporation), the portion of any RSU that is unvested shall fully vest and become immediately exercisable in the event of a Change in Control Termination (as defined below). This right to accelerated vesting shall in no way (i) limit the Board's discretion to take the actions set forth in Section 9(c) of the Plan in the event of a Transaction, or (ii) alter other terms of this RSU Agreement.

As used herein: "Change in Control Termination" means termination of your employment by the Company (or any surviving or acquiring corporation or entity) within twelve months of a Change in Control where such termination is without Cause or results from your resignation for Good Reason; and "Good Reason" means any of the following actions taken by the Company (or any surviving or acquiring corporation or entity) without your consent: (i) any material diminution of your authority, duties or responsibilities; (ii) a material (greater than ten percent (10%)) reduction by the Company (or any surviving or acquiring corporation or entity) of your Base Salary except in the case of across-the-board salary reductions similarly affecting all or substantially all similarly-situated employees of the Company or any surviving or acquiring corporation or entity); (iii) a relocation of your place of employment to a location in excess of

fifty (50) miles from the Company's last known principal place of employment; *provided, however,* that it will only be deemed Good Reason if (1) prior to your resignation, the Company (or any surviving or acquiring corporation or entity) has not previously notified you of its intention to terminate your employment; (2) the Company (or any surviving or acquiring corporation or entity) is given written notice from you within ninety (90) days following the first occurrence of a condition that you consider to constitute Good Reason (with such notice including a description of the condition); (3) the Company (or any surviving or acquiring corporation or entity) fails to remedy such condition within thirty (30) days following such written notice, and (4) you resign from employment effective not later than fourteen (14) days after the end of the cure period. Notwithstanding the foregoing, any actions taken to accommodate a disability of you or pursuant to the Family and Medical Leave Act or an applicable state leave law will not be a Good Reason for purposes of this Agreement.

18. **MISCELLANEOUS.**

(a) The rights and obligations of the Company under your Award shall be transferable by the Company to any one or more persons or entities, and all covenants and agreements hereunder shall inure to the benefit of, and be enforceable by, the Company's successors and assigns.

(b) You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your Award.

(c) You acknowledge and agree that you have reviewed your Award in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your Award and fully understand all provisions of your Award.

(d) This Agreement shall be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

(e) All obligations of the Company under the Plan and this Agreement shall be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

19. **GOVERNING PLAN DOCUMENT.** Your Award is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your Award, and is further subject to all interpretations, amendments, and rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. Except as expressly provided herein, if there is any conflict between the provisions of the Award and those of the Plan, the provisions of the Plan will control. Your Award (and any compensation paid or shares issued under your Award) is subject to recoupment in accordance with The Dodd-Frank Wall Street Reform and Consumer Protection Act and any implementing regulations thereunder, any compensation recovery policy otherwise required by applicable law and any recoupment or clawback policy adopted by the

Company (whether or not required by applicable law). No recovery of compensation under such a clawback policy will be an event giving rise to a right to voluntarily terminate employment upon a resignation for "good reason," or for a "constructive termination" or any similar term under any plan of or agreement with the Company.

20. **EFFECT ON OTHER EMPLOYEE BENEFIT PLANS.** The value of the Award subject to this Agreement shall not be included as compensation, earnings, salaries or other similar terms used when calculating benefits under any employee benefit plan (other than the Plan) sponsored by the Company or any Affiliate except as such plan otherwise expressly provides. The Company expressly reserves its right to amend, modify, or terminate any or all of the employee benefit plans of the Company or any Affiliate.

21. **SEVERABILITY.** If all or any part of this Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid such unlawfulness or invalidity shall not invalidate any portion of this Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Agreement (or part of such a Section) so declared to be unlawful or invalid shall, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

22. **OTHER DOCUMENTS.** You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act. In addition, you acknowledge receipt of the Company's policy permitting certain individuals to sell shares only during certain "window" periods and the Company's insider trading policy, in effect from time to time.

23. **AMENDMENT.** This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that, except as otherwise expressly provided in the Plan, no such amendment materially adversely affecting your rights hereunder may be made without your written consent. Without limiting the foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the Award as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change shall be applicable only to rights relating that portion of the Award which is then subject to restrictions as provided herein.

24. **SECTION 409A OF THE CODE.** This Award is intended to be exempt from the application of Section 409A of the Code, including but not limited to by reason of complying with the "short-term deferral" rule set forth in Treasury Regulation Section 1-409A-1(b)(4) and will be construed and administered in such a manner any ambiguities herein shall be interpreted accordingly. Notwithstanding the foregoing, if it is determined that the Award fails to satisfy the requirements of the short-term deferral rule and is otherwise not exempt from, and determined to be deferred compensation subject to Section 409A of the Code, this Award shall comply with

Section 409A to the extent necessary to avoid adverse personal tax consequences and any ambiguities herein shall be interpreted accordingly.

Notwithstanding anything in this Agreement to the contrary, if this Award is subject to Section 409A of the Code and any shares otherwise are issuable under this Award in connection with your termination of employment with the Company, then such shares will not be issuable unless such termination constitutes a "separation from service" (as such term is defined in Treasury Regulations Section 1.401A-1(h) without regard to any alternative definition thereunder) ("**Separation from Service**"). Notwithstanding anything in this Agreement to the contrary, if it is determined that the Award is deferred compensation subject to Section 409A and you are a "specified employee" (within the meaning set forth in Section 409A(a)(2)(B)(i) of the Code) as of the date of your Separation from Service, then the issuance of any shares that would otherwise be made upon the date of your Separation from Service or within the first six (6) months thereafter will not be made on the originally scheduled date(s) and will instead by issued in a lump sum on the earlier of (i) the date that is six (6) months and one day after the date of the Separation from Service and (ii) the date of your death, with the balance of the shares issued thereafter in accordance with the original vesting and issuance schedule as per this Agreement, but if and only if such delay in the issuance of the shares is necessary to avoid the imposition of adverse taxation on you in respect of the shares under Section 409A of the Code. Each installment of shares that vests is intended to constitute a "separate payment" for purposes of Treasury Regulation Section 1.409A-2(b)(2). Notwithstanding any contrary provision of the Plan, the Grant Notice or of this Agreement, under no circumstances will the Company reimburse you for any taxes or other costs under Section 409A of the Code or any other tax law or rule. All such taxes and costs are solely your responsibility.

This Restricted Stock Unit Award Agreement shall be deemed to be signed by the Company and the Participant upon the signing by the Participant of the Restricted Stock Unit Grant Notice to which it is attached.

EXHIBIT B TO UNANIMOUS WRITTEN CONSENT DATED NOVEMBER 10, 2021

MEMORANDUM

To: [Recipient] (“Recipient”)

From: [Manager]

Date: [Date]

Re: Retention Bonus Award

This memorandum confirms the Retention Bonus Award approved by the Board of Directors of Entasis Therapeutics Holdings Inc. on November 10, 2021, as follows:

Award Amount(1)	Payment Date	Conditions to Award
$ XXXX	50% on six month anniversary of Change in Control 50% on twelve month anniversary of Change in Control	In the event of a Change in Control, each installment of the Award Amount will become due and payable as soon as practicable after each Payment Date, on the condition that the Recipient maintains Continuous Service through each Payment Date. In the event Recipient incurs a Change in Control Termination(2), any portion of the Award Amount that has not been paid as of the date of the Change in Control Termination shall be paid as soon as practicable after such date.

This Retention Bonus Award is being issued under the 2018 Equity Incentive Plan (the “Plan”). All of the terms and conditions of the Plan, which is attached hereto, are incorporated herein in their entirety. Capitalized terms not defined herein but defined in the Plan will have the same definitions as in the Plan. If there is any conflict between this award agreement and the Plan, the terms of the Plan will control.

(1) Represents gross amount of award. Applicable tax withholdings and deductions will be calculated on the date of payment.

(2) Change in Control Termination has the meaning set forth in the Amendment to Option Award dated November 10, 2021 under the Plan.

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, Manoussos Perros, certify that:

1. I have reviewed this Annual Report on Form 10-K of Entasis Therapeutics Holdings Inc.;

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(s) 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) 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

(d) 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(s) 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 3, 2022

By: /s/ Manoussos Perros, Ph.D.
Manoussos Perros, Ph.D.
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, Kristie Wagner, certify that:

1. I have reviewed this Annual Report on Form 10-K of Entasis Therapeutics Holdings Inc.;

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(s) 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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) 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

(d) 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(s) 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 3, 2022

By: /s/ Kristie Wagner
Kristie Wagner
Vice President Corporate Controller
(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 Entasis Therapeutics Holdings Inc. (the "Company") for the year ended December 31, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers of the Company hereby certifies, pursuant to 18 U.S.C. Section 1350, that to his or her knowledge:

(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 3, 2022

By: /s/ Manoussos Perros, Ph.D.
Manoussos Perros, Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

Date: March 3, 2022

By: /s/ Kristie Wagner
Kristie Wagner
Vice President Corporate Controller
(Principal Financial and Accounting Officer)